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# Anesthesia and Analgesia

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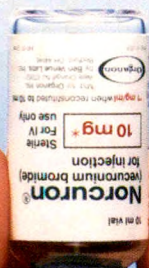


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# Anesthesia and Analgesia

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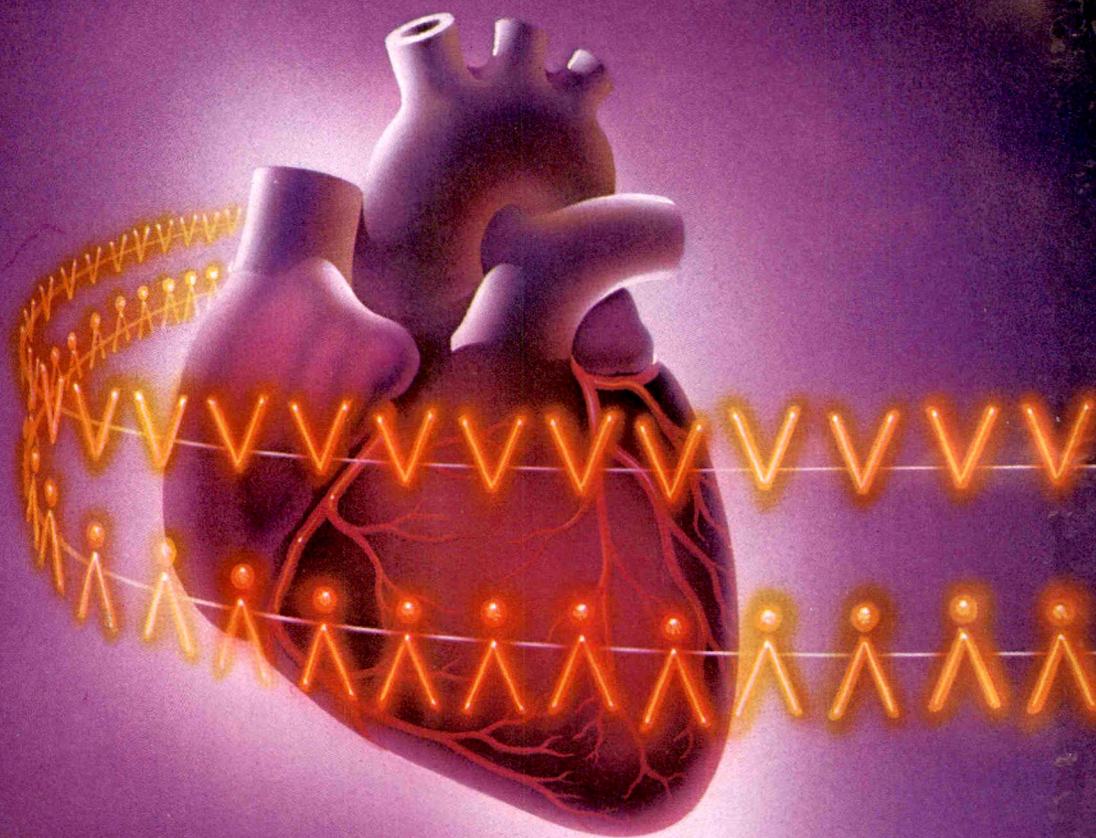
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**CONTRAINDICATIONS:** SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS:** SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

**An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.**

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following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8  $\mu\text{g}/\text{kg}$ ) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8  $\mu\text{g}/\text{kg}$ ). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

**PRECAUTIONS: General:** The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to  $\text{CO}_2$  stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion



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**Pregnancy Category C:** SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

**Animal Toxicology:** The intravenous LD<sub>50</sub> of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

**ADVERSE REACTIONS:** The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia  
Gastrointestinal: nausea, vomiting  
Respiratory: apnea, postoperative respiratory depression, bronchospasm

Dermatological: itching, erythema  
Central Nervous System: chills  
Miscellaneous: intraoperative muscle movement

**DRUG ABUSE AND DEPENDENCE:** SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

**OVERDOSAGE:** Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD<sub>50</sub> of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD<sub>50</sub>s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

**DOSAGE AND ADMINISTRATION:** The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).



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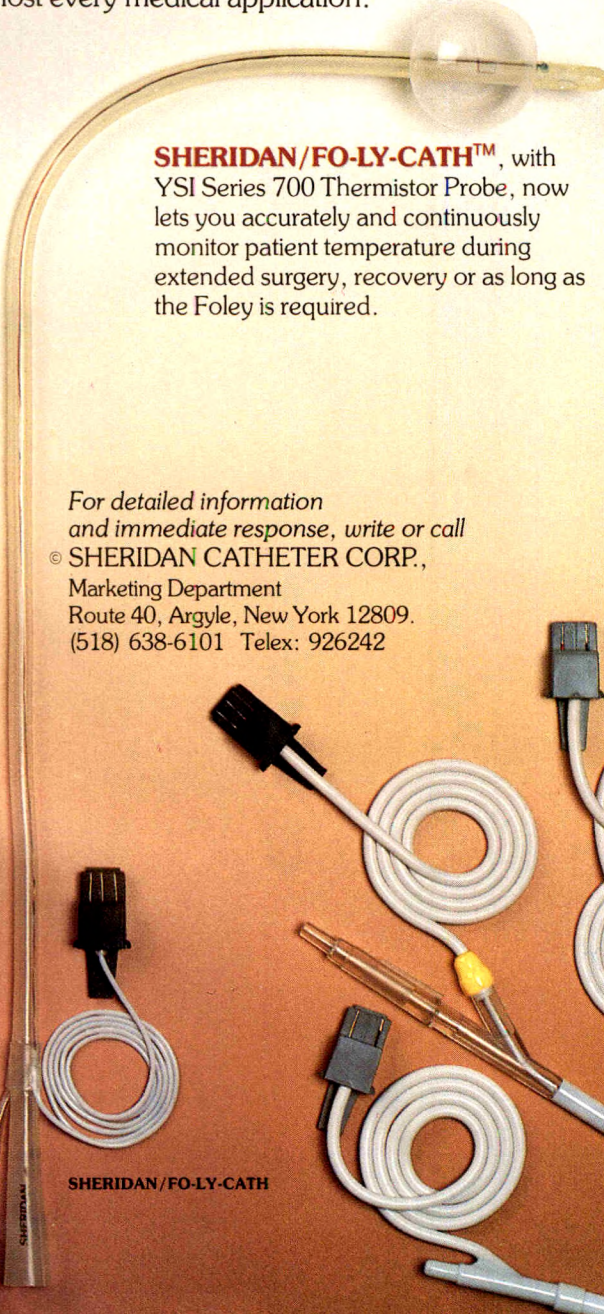
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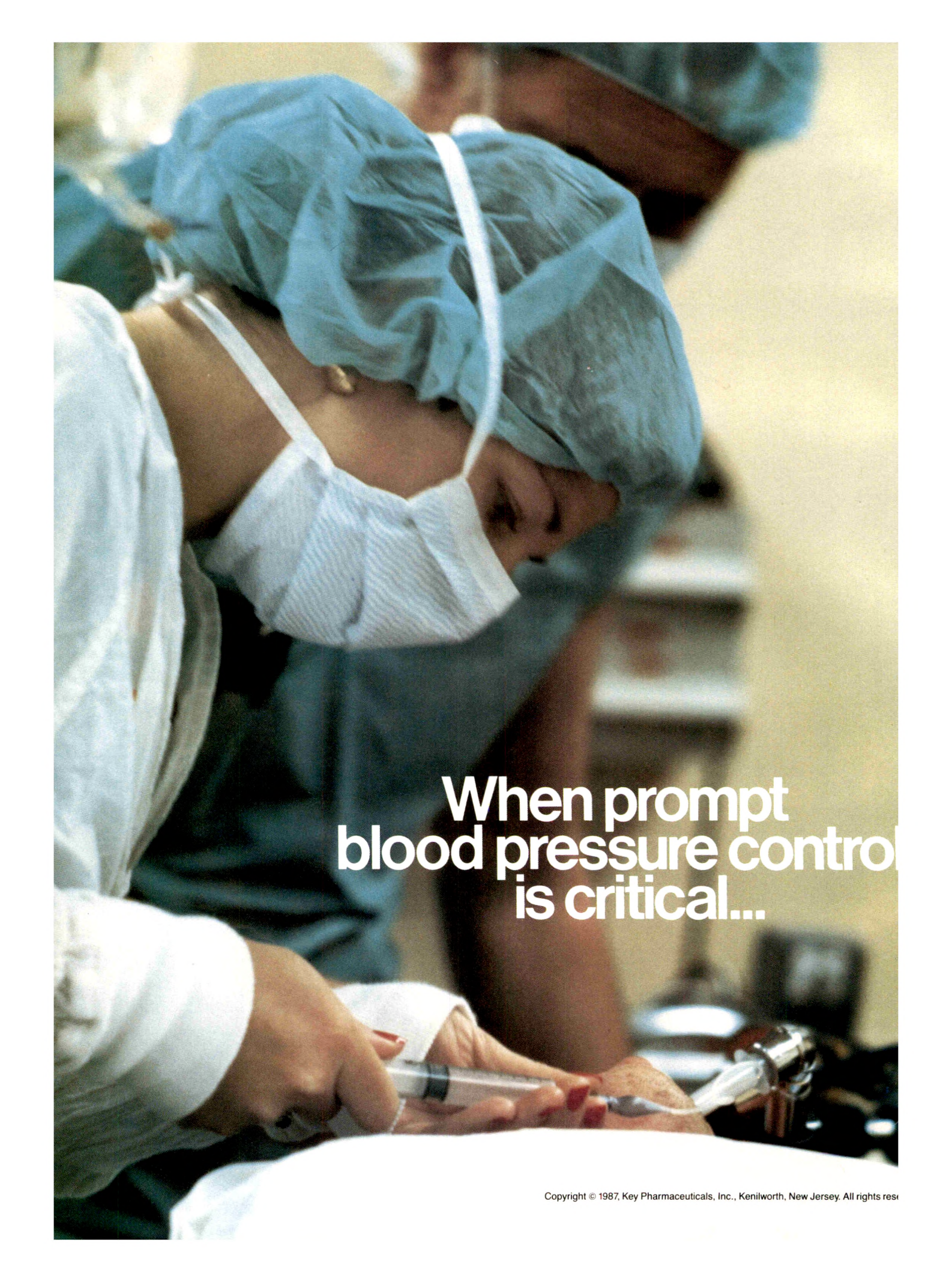
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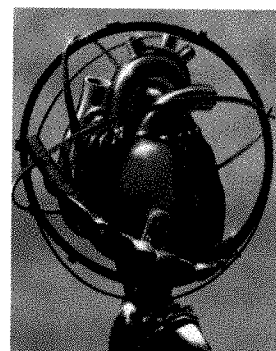


A close-up, slightly high-angle shot of a surgeon in a sterile operating room. The surgeon is wearing a light blue bouffant cap and a white surgical mask, with only their eyes visible. They are wearing white gloves and are focused on a patient's arm. The patient's arm is resting on a white surface, and the surgeon is holding a clear plastic syringe, preparing to administer medication. The background is blurred, showing other parts of the operating room and another person in blue scrubs.

**When prompt  
blood pressure control  
is critical...**



Intravenous  
**NORMODYNE**<sup>®</sup>  
(labetalol HCl) Injection  
5 mg/mL



**Lowers critically  
high blood pressure...  
promptly...smoothly...  
reliably**

- onset of response in five to ten minutes
- can be carefully controlled  
little risk of "overshoot"

The blood pressure should be monitored during and after completion of the infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic blood pressure during intravenous treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as indicator of effectiveness in addition to the response of the diastolic pressure.

- cardiac output maintained  
helps assure vital organ perfusion
- helps prevent reflex tachycardia
- no intra-arterial monitoring required
- no toxic metabolite  
avoids cyanide toxicity
- easy to administer

Because symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within three hours of intravenous administration of labetalol, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

For Brief Summary, please see next page.



# NORMODYNE®

## brand of labetalol hydrochloride

### Injection

#### BRIEF SUMMARY

##### INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.

##### CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia. (See WARNINGS.)

##### WARNINGS

**Cardiac Failure:** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

**Patients Without a History of Cardiac Failure:** In patients with latent cardiac insufficiency, continued depression of the myocardium with long-term therapy over a period of time can in some cases lead to cardiac failure. At the first sign or symptoms of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuresis, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

**Ischemic Heart Disease:** Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of NORMODYNE is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina suddenly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be discontinued promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

**Neurologic Bronchospasm:** (e.g., chronic bronchitis and emphysema). Since NORMODYNE (labetalol HCl) Injection at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

**Pharmacologic Inhibition:** Intravenous labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

**Diabetic Mellitus and Hypoglycemia:** Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetes. Beta-blockade also reduces the release of insulin in response to hypoglycemia; it may therefore be necessary to adjust the dose of anti-diabetic drugs.

**Major Surgery:** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protected severe hypotension and difficulty in restarting a heart beat have been reported with beta-blockers. The effect of labetalol HCl on alpha-adrenergic activity has not been evaluated in this setting.

**Myocardial Infarction:** A synergism between labetalol HCl and halothane anesthesia has been shown (see Drug Interactions). **Rapid Decreases of Blood Pressure:** Caution must be observed when reducing severely elevated blood pressure. Although such findings have not been reported with intravenous labetalol HCl, a number of adverse reactions, including cerebral infarction, optic nerve infarction, angina and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as one or two days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

##### PRECAUTIONS

**General Impaired Hepatic Function:** may diminish metabolism of NORMODYNE (labetalol HCl) Injection.

**Hypotension:** Symptomatic postural hypotension (incidence 50%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving NORMODYNE (labetalol HCl) Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

**Jaundice or Hepatic Dysfunction:** On rare occasions, oral labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately, should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

##### Information for Patients

The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) NORMODYNE Injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of ambulation.

When the patient is started on NORMODYNE Tablets, following adequate control of blood pressure with NORMODYNE Injection, appropriate directions for timing of dosage should be provided. (See DOSAGE AND ADMINISTRATION.)

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see ADVERSE REACTIONS).

##### Laboratory Tests

Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

##### Drug Interactions

Since NORMODYNE (labetalol HCl) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The combination of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-agonist bronchodilator drugs in patients with bronchospasm; therefore, doses greater than the normal and standard dose of beta-agonist bronchodilator drugs may be required.

Caution has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotension anesthesia with labetalol HCl in association with halothane, high concentrations (1% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

##### Drug/Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioimmunoassay or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

##### Cardiovascular, Musculoskeletal, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenicity. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenicity.

##### Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

##### Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

##### Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

##### Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE (labetalol HCl) Injection is administered to a nursing woman.

##### Pediatric Use

Safety and effectiveness in children have not been established.

##### ADVERSE REACTIONS

NORMODYNE (labetalol HCl) Injection is usually well tolerated. Most adverse effects have been mild and transient and in controlled trials involving 92 patients did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 50%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving NORMODYNE (labetalol HCl) Injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with NORMODYNE Injection with the incidence per 100 patients as noted:

- Cardiovascular System: Ventricular arrhythmias in 1.
- Cerebral and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/tingle 7; hyposthesia (numbness), and vertigo 1 each.
- Gastrointestinal System: Nausea in 13; vomiting 4; dyspepsia and taste disorder, 1 each.
- Mesothelial Disorders: Thrombocytopenia in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drugs in blood pressure, generally in patients with prior renal insufficiency.
- Psychiatric Disorders: Somnolence/sleeping in 3.
- Respiratory System: Wheezing in 1.
- Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see NORMODYNE Tablets Product Information for details). Certain of the side effects increased with increasing oral dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600	800	900	1200	1600	2400
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Flushing	<1	0	4	4	5	3	3	6	10
Nausea	<1	0	<1	<1	4	0	7	11	19
Vomiting	0	0	<1	<1	0	1	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Parosmia	2	0	2	2	1	1	2	5	5
Nasal Stiffness	1	1	2	2	2	2	4	5	6
Flaccidation Failure	0	2	1	2	3	0	4	3	3
Impotence	1	0	1	1	2	4	4	4	5
Edema	1	0	1	1	1	0	1	2	2

The oculocardiac syndrome associated with the beta-blocker piroxicol has not been reported with labetalol HCl during investigation with drugs in blood pressure.

**Clinical Laboratory Tests:** Among patients dosed with NORMODYNE (labetalol HCl) Tablets, there have been reversible increases of serum creatinine in 4% of patients treated, and more rarely, reversible increases in blood urea.

##### OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Injection causes excessive hypotension that is posture sensitive, and sometimes, excessive bradycardia. Patients should be placed supine and their legs raised if necessary to improve the blood supply to the brain. If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) may be useful for removal of the drug shortly after ingestion. The following additional measures should be employed if necessary: Excessive bradycardia—administer atropine or epinephrine. Cardiac failure—administer a digitalis glycoside and a diuretic. Dopamine or dobutamine may also be useful. Hypotension—administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. Bronchospasm—administer epinephrine and/or an aerosolized beta-agonist. Seizures—administer diazepam.

Since beta-blocker overdosage in hypotension and bradycardia has been shown to be effective when administered in large doses (5 to 10 mg rapidly over 30 seconds, followed by continuous infusion of 5 mg/hr that can be reduced as the patient improves).

Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol HCl from the general circulation (<1%).

The oral LD<sub>50</sub> value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD<sub>50</sub> in these species is 50 to 60 mg/kg.

##### DOSAGE AND ADMINISTRATION

NORMODYNE (labetalol HCl) Injection is intended for intravenous use in hospitalized patients. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

Patients should always be kept in a supine position during the period of intravenous drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position should be established before permitting any ambulation, such as using toilet facilities.

Either of two methods of administration of NORMODYNE Injection may be used: a) repeated intravenous injections, b) slow continuous infusion.

**Repeated intravenous injection:** Initially, NORMODYNE (labetalol HCl) Injection should be given in a dose of 20 mg labetalol HCl (which corresponds to 0.25 mg/ml for an 80 kg patient) by slow intravenous injection over a two-minute period. Immediately before the injection and at five and ten minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 mg or 80 mg can be given at ten minutes intervals until a desired supine blood pressure is achieved or a total of 300 mg labetalol HCl has been injected. The maximum effect usually occurs within 5 minutes of each injection.

**Slow Continuous Infusion:** NORMODYNE (labetalol HCl) Injection is prepared for intravenous continuous infusion by diluting the contents with commonly used intravenous fluids (see below). Examples of methods of preparing the infusion solution are:

The contents of either two 20 ml vials (40 ml), or one 40 ml vial, are added to 160 ml of a commonly used intravenous fluid such that the resultant 200 ml of solution contains 200 mg of labetalol HCl, 1 mg/ml. The diluted solution should be administered at a rate of 2 ml/min to deliver 2 mg/min.

Alternatively, the contents of either two 20 ml vials (40 ml), or one 40 ml vial, of NORMODYNE (labetalol HCl) Injection are added to 250 ml of a commonly used intravenous fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2 mg/3 ml. The diluted solution should be administered at a rate of 3 ml/min to deliver approximately 2 mg/min.

The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion, the diluted solution can be infused using a controlled administration mechanism, e.g., graduated burette or mechanically driven infusion pump.

Since the half-life of labetalol is 5 to 8 hours, steady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should be stopped and oral labetalol HCl started (see below). The effective intravenous dose is usually in the range of 50 to 300 mg. A total dose of up to 300 mg may be required in some patients.

**Blood Pressure Monitoring:** The blood pressure should be monitored during and after completion of the infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic blood pressure during intravenous treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as indicator of effectiveness in addition to the response of the diastolic pressure.

**Initiation of Dosing with NORMODYNE Tablets:** Subsequent oral dosing with NORMODYNE (labetalol HCl) Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 or 400 mg, depending on the blood pressure response. Thereafter, individualization with NORMODYNE (labetalol HCl) Tablets may proceed as follows:

Regimen	Inpatient Titration Instructions	Daily Dose*
200 mg bid		400 mg
400 mg bid		800 mg
800 mg bid		1600 mg
1200 mg bid		2400 mg

\*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of NORMODYNE Tablets may be increased at one day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing see NORMODYNE Tablets Product Information DOSAGE AND ADMINISTRATION for additional recommendations.

##### Compatibility with commonly used intravenous fluids

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

NORMODYNE (labetalol HCl) Injection was tested for compatibility with commonly used intravenous fluids at final concentrations of 1.25 mg to 3.75 mg labetalol HCl per ml of the mixture. NORMODYNE Injection was found to be compatible with and stable (for 24 hours refrigerated or at room temperature) in mixtures with the following solutions:

- Ringers Injection, USP
- Lactated Ringers Injection, USP
- 5% Dextrose and Ringers Injection
- 5% Lactated Ringers and 5% Dextrose Injection
- 5% Dextrose Injection, USP
- 0.9% Sodium Chloride Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- 2.5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- 5% Dextrose and 0.33% Sodium Chloride Injection, USP

NORMODYNE (labetalol HCl) Injection was NOT compatible with 5% Sodium Bicarbonate Injection, USP.

##### HOW SUPPLIED

NORMODYNE (labetalol HCl) Injection, 5 mg/ml, is supplied in 20 ml (100 mg) (NDC-0085-0362-07) and 40 ml (200 mg) (NDC-0085-0362-08) multi-dose vials, boxes of 1.

Store between 2° and 30°C (36° and 86°F). Do not freeze.

**KEM** Key Pharmaceuticals, Inc.  
Kendallville, NJ 07033 USA

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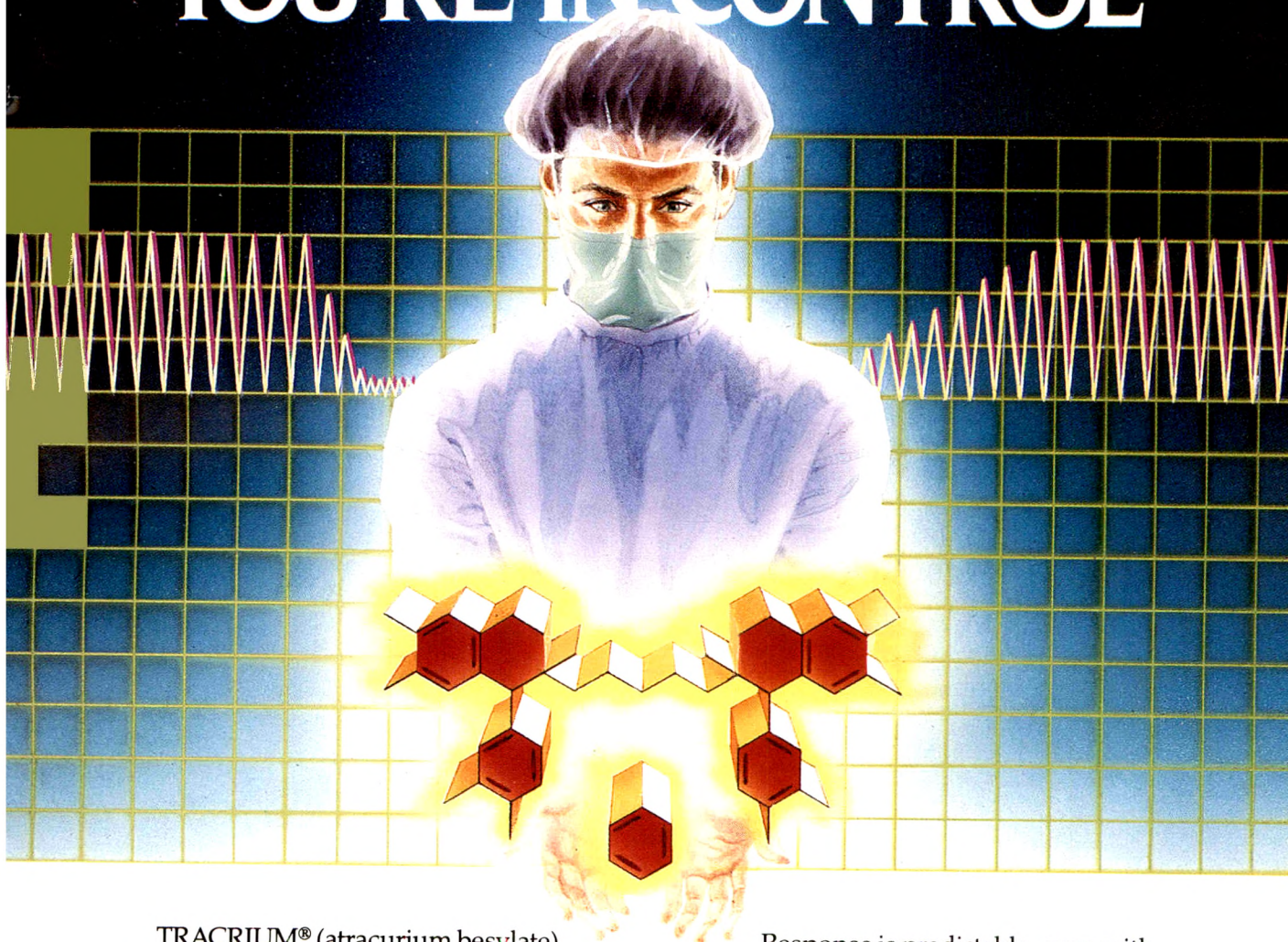
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TRACRIUM® (atracurium besylate) Injection is meaningfully different from all other neuromuscular blockers. TRACRIUM is inactivated in plasma by two pathways, Hofmann elimination and ester hydrolysis, that act independently of liver or kidney function. This unique metabolism can result in *superior control* and makes possible:

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Repeated equipotent doses of TRACRIUM, administered at equal intervals, have no cumulative effect.<sup>2</sup>

Response is predictable, even with multiple injections or long periods of continuous infusion,<sup>3</sup> allowing you additional time for patient monitoring.

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■ **More Predictable, Superior Control**

TRACRIUM is an excellent agent for administration by repeated bolus injection or continuous infusion. The lack of cumulative effects of TRACRIUM by infusion makes possible a smooth, steady-level relaxation without the need for multiple maintenance bolus doses throughout a long procedure.

## TRACRIUM® INJECTION

(atracurium besylate)



## TRACRIUM® INJECTION (atracurium besylate)

### Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

### PRECAUTIONS:

**General:** Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

**Pregnancy, Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

### ADVERSE REACTIONS:

**Observed in Controlled Clinical Studies:** Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of  $\geq 0.60$  mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses  $\leq 0.30$  mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.


**Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: **General:** allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); **Musculoskeletal:** inadequate, prolonged block; **Cardiovascular:** hypotension, vasodilatation (flushing), tachycardia, bradycardia; **Respiratory:** dyspnea, bronchospasm, laryngospasm; **Integumentary:** rash, urticaria, injection site reaction.

<sup>1</sup>Miller R, Rupp S, Fisher D, et al: Clinical pharmacology of vecuronium and atracurium. *Anesth* 1984;61:444-453.

<sup>2</sup>Payne J: Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*. Orlando, Grune & Stratton, 1984, p 98.

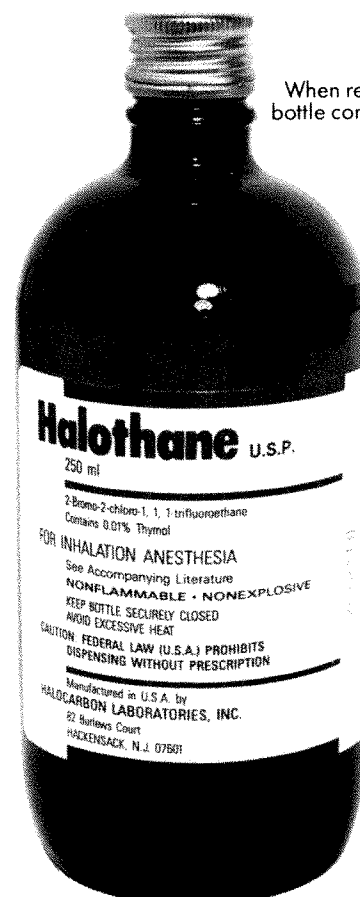
<sup>3</sup>Eagar B, Flynn P, Hughes R: Infusion of atracurium for long surgical procedures. *Br J Anaesth* 1984;56:447-452.

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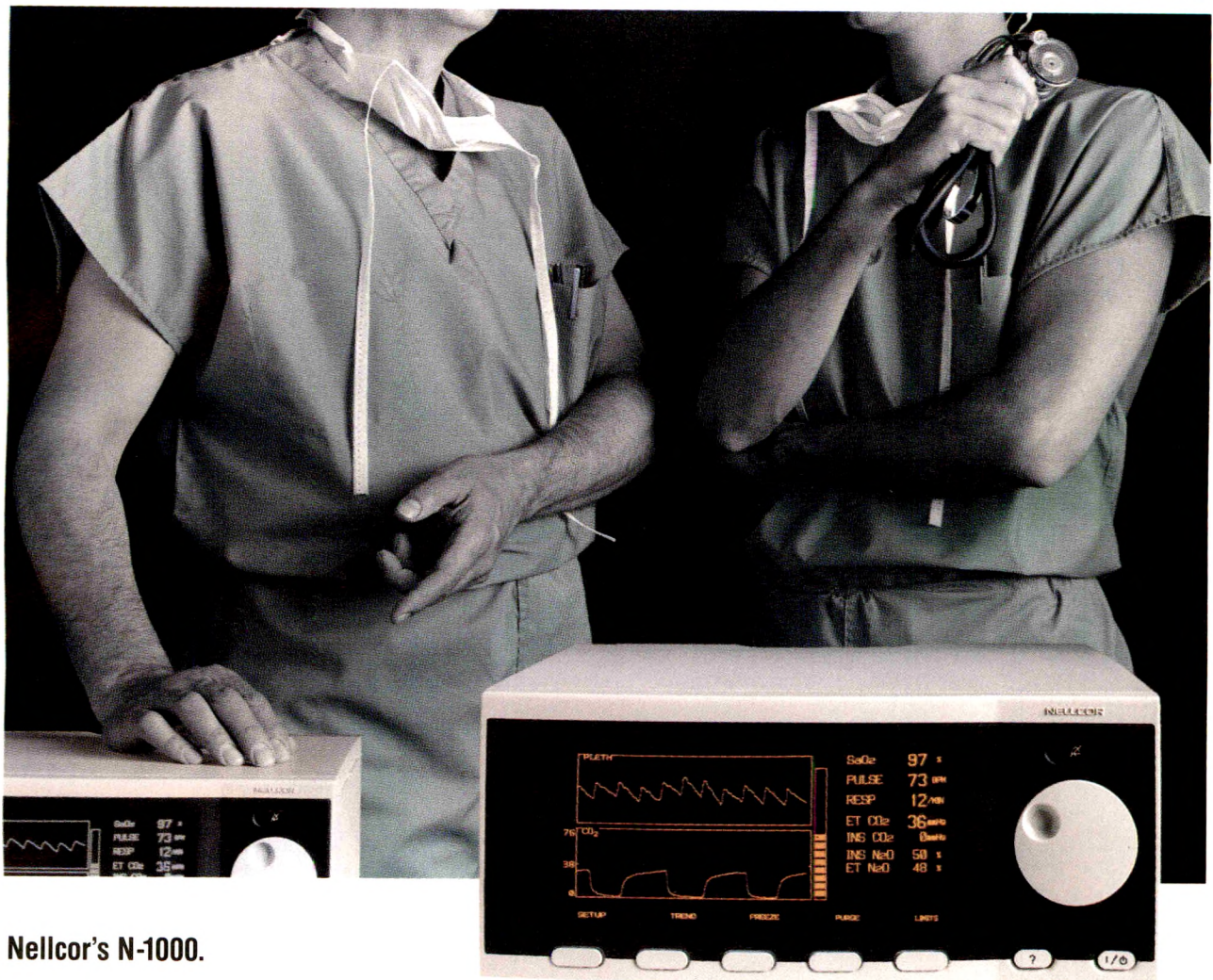
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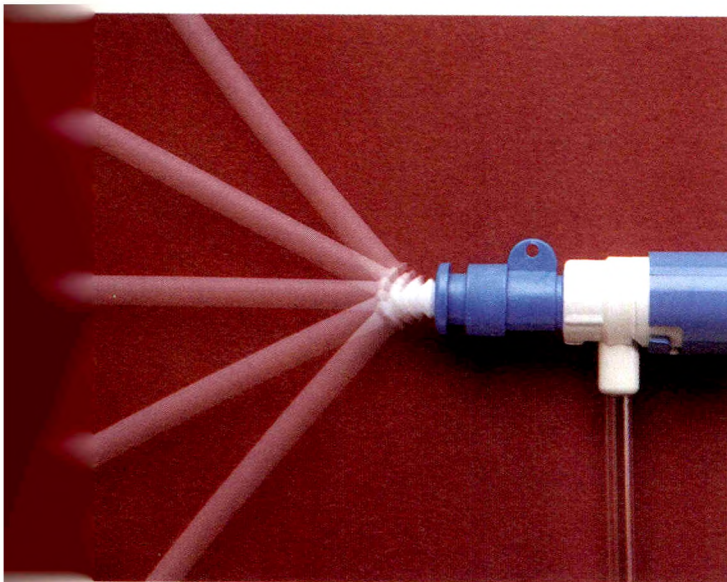






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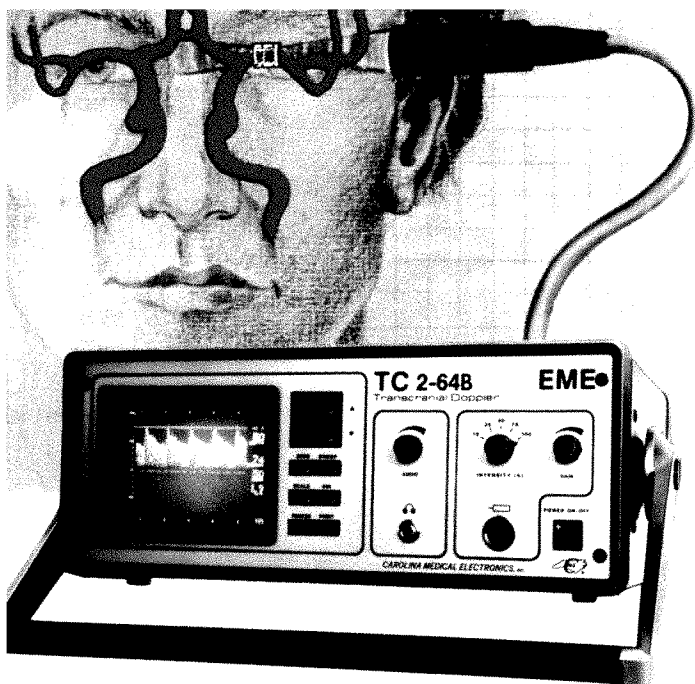
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**In neuromuscular  
blockade:  
Greater safety  
begins where the  
similarities end.**



**Atracurium**

A close-up, black and white photograph of a medical syringe. The syringe is angled diagonally from the bottom left towards the top right. The needle is long and thin, pointing towards the upper right corner of the frame. The syringe barrel has some markings, but they are not clearly legible. The background is a light, textured surface.



**Norcuron<sup>®</sup>**  
(vecuronium bromide) for injection

A close-up, black and white photograph of a medical syringe, similar to the one above. It is also angled diagonally from the bottom left towards the top right. The needle is long and thin, pointing towards the upper right corner. The syringe barrel has markings, and the text 'Norcuron' and '(vecuronium bromide) for injection' is printed on it. The background is a light, textured surface.

See last page for brief summary of prescribing information on NORCURON<sup>®</sup>.



**The  
similarities:**

**The  
Norcuron<sup>®</sup>  
difference:**

**Short,  
intermediate,  
and long  
procedures.**

**Continuous  
infusion.**

**Free of  
clinically  
significant  
cardiovascular  
effects.**

**High-  
dose  
safe**





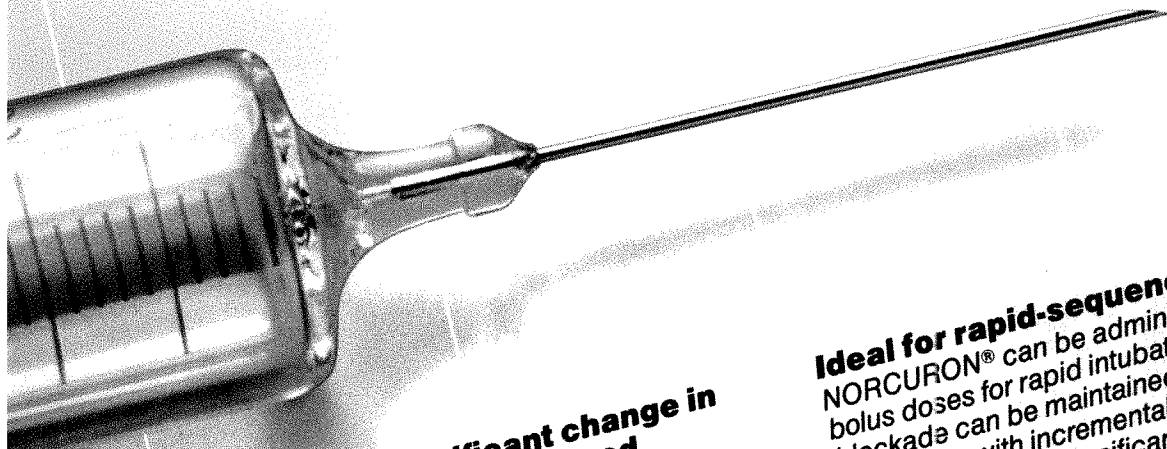
**Polypharmacy  
avoided.**

**Histamine  
release  
unlikely.**

**No  
refrigeration.**

**Stability/  
potency  
assured.**

**Free from  
potentially  
toxic  
metabolites.**



**Little risk of significant change in  
heart rate and arterial blood  
pressure.**

Even at  $3.5 \times ED_{95}$ , there is a wide safety margin between assayed plasma histamine concentrations and levels at which significant changes in arterial pressure and heart rate are known to occur.<sup>1,2</sup>

**Choose the technique you  
prefer for longer procedures.**

Either continuous infusion for smooth, steady-state relaxation or high initial bolus dosing.

**For virtually all your patients.**

The only neuromuscular blocking agent virtually free of clinically significant cardiovascular and histamine-related side effects.<sup>1,3-6</sup> For patients with significant cardiovascular disease, asthmatics and others in whom substantial histamine release would be hazardous, the elderly, infants, and outpatients.

**Ideal for rapid-sequence induction.**  
NORCURON® can be administered in high bolus doses for rapid intubation,<sup>7</sup> and blockade can be maintained throughout the procedure with incremental doses of the same agent. This significantly simplifies dosing, monitoring, and administration and avoids the complications of polypharmacy.

Since atracurium cannot be easily administered in high doses without risk of histamine-related side effects, use of an additional agent is usually required for rapid intubation.<sup>8</sup>

**Room temperature stability.**

No refrigeration required. Lyophilized NORCURON® reconstituted at surgery assures optimal potency.

See next page for brief summary of prescribing information on NORCURON®.

**Norcuron® where safety begins.**  
(vecuronium bromide) for injection

P 24, 567



# Norcuron<sup>®</sup>

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

**THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.**

## CONTRAINDICATIONS:

**WARNINGS:** NORCURON<sup>®</sup> SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron<sup>®</sup> may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

**PRECAUTIONS: Renal Failure:** Norcuron<sup>®</sup> is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for nonlethal surgery, a lower initial dose of Norcuron<sup>®</sup> should be considered.

**Altered Circulation Time:** Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

**Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron<sup>®</sup> metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

**Severe Obesity or Neuromuscular Disease:** Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron<sup>®</sup>.

**Malignant Hyperthermia:** Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron<sup>®</sup> is capable of triggering malignant hyperthermia.

Norcuron<sup>®</sup> has no known effect on consciousness, the pain threshold, or cerebation. Administration must be accompanied by adequate anesthesia.

**Drug Interactions:** Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron<sup>®</sup> (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron<sup>®</sup>, the administration of Norcuron<sup>®</sup> should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04 to 0.06 mg/kg of Norcuron<sup>®</sup> may be administered to produce complete neuromuscular block with clinical duration of action of 25 to 30 minutes. The use of Norcuron<sup>®</sup> before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron<sup>®</sup>; therefore these drugs and Norcuron<sup>®</sup> may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron<sup>®</sup> and other competitive muscle relaxants in the same patient.

**Inhalational Anesthetics:** Use of volatile inhalational anesthetics with Norcuron<sup>®</sup> will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron<sup>®</sup> may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

**Antibiotics:** Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

**Other:** Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron<sup>®</sup>. Norcuron<sup>®</sup> induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

## Drug/Laboratory Test Interactions:

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted with Norcuron<sup>®</sup>. Norcuron<sup>®</sup> should be given to a pregnant woman only if clearly needed.

**Pediatric Use:** Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron<sup>®</sup> on a mg/kg basis than adults and take about 1 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

**ADVERSE REACTIONS:** Norcuron<sup>®</sup> was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron<sup>®</sup> as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron<sup>®</sup> is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

**OVERDOSAGE:** There has been no experience with Norcuron<sup>®</sup> overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron<sup>®</sup> can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron<sup>®</sup> as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates, and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol<sup>®</sup> (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate, will usually antagonize the skeletal muscle relaxant action of Norcuron<sup>®</sup>. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

**DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information.** Norcuron<sup>®</sup> (vecuronium bromide) for injection is for intravenous use only. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron<sup>®</sup> by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron<sup>®</sup> and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron<sup>®</sup> is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED<sub>50</sub>) given as an

## Norcuron<sup>®</sup> (vecuronium bromide) for injection

intravenous bolus injection. This dose can be expected to produce good or excellent nonemergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25 to 30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45 to 65 minutes after injection. In the presence of potent inhalational anesthetics, the neuromuscular blocking effect of Norcuron<sup>®</sup> is enhanced. If Norcuron<sup>®</sup> is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron<sup>®</sup> dose may be reduced by approximately 15%, ie, 0.060 to 0.085 mg/kg. Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron<sup>®</sup>. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron<sup>®</sup> to 0.04 to 0.06 mg/kg with inhalation anesthesia and 0.05 to 0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron<sup>®</sup> are recommended; after the initial Norcuron<sup>®</sup> injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron<sup>®</sup> lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

**Use by Continuous Infusion:** After an intubating dose of 80 to 100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20 to 40 minutes later. Infusion of Norcuron<sup>®</sup> should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations.

The infusion of Norcuron<sup>®</sup> should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25 to 60%, 45 to 60 minutes after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron<sup>®</sup> infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron<sup>®</sup> can be prepared by mixing Norcuron<sup>®</sup> with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringer's. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron<sup>®</sup> can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

\* 10 mg of Norcuron<sup>®</sup> in 100 mL solution.

† 20 mg of Norcuron<sup>®</sup> in 100 mL solution.

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON <sup>®</sup> Infusion Rate (mL/min)								
Amount of Drug (µg/kg/min)	Patient Weight (kg)							
	40	50	60	70	80	90	100	
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70	
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80	
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90	
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00	
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10	
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20	
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30	

**Note:** If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

**Dosage in Children:** Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron<sup>®</sup> on a mg/kg basis than adults and take about 1 1/2 times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore no dosing recommendation can be made.

**COMPATIBILITY:** Norcuron<sup>®</sup> (vecuronium bromide) for injection is compatible in solution with:

0.9% NaCl solution  
5% glucose in water  
5% glucose in saline  
Lactated Ringer's  
Sterile water for injection

Use within 8 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**HOW SUPPLIED:** 10 mL vials (10 mg of vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP), 22 g 1 1/4" needle. Boxes of 10 (NDC #0052-0441-60).

5 mL vials (10 mg vecuronium bromide) and 5 mL vials of diluent (bacteriostatic water for injection, USP).

Boxes of 10 (NDC #0052-0440-17).

10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP).

Boxes of 10 (NDC #0052-0441-17).

10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED. Boxes of 10 (NDC #0052-0441-15).

Rev. 1/88

## Greater flexibility NOW BY CONTINUOUS INFUSION

**References:** 1. Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. 2. Scott RPF, Savarese JJ: The cardiovascular and autonomic effects of neuromuscular blocking agents. *Semin Anesth* 1984; 3:319-334. 3. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary bypass grafting. *Anesthesiology* 1983; 58:438-440. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. 5. Durant NN: NORCURON<sup>®</sup>: a new nondepolarizing blocking agent. *Semin Anesth* 1982; 1:47-56. 6. Krieg N, Crul JF, Booy LHDJ: Relative potency of Org NC45, pancuronium, alcuronium and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. 7. Lennon RL, Olson RA, Gronert GA: Attraction or vecuronium for rapid sequence endotracheal intubation. *Anesthesiology* 1986; 64:510-513. 8. Scott RPF, et al: Clinical pharmacology of atracurium given in high dose. *Br J Anaesth* 1986; 58:834-838.



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# Eye Guard

Patent Pending

- Protects patient's eyes from contact with drapes
- Shields patient's eyes from debris or accidental injury
- Seals to promote a 'Greenhouse' effect to keep eyes moist

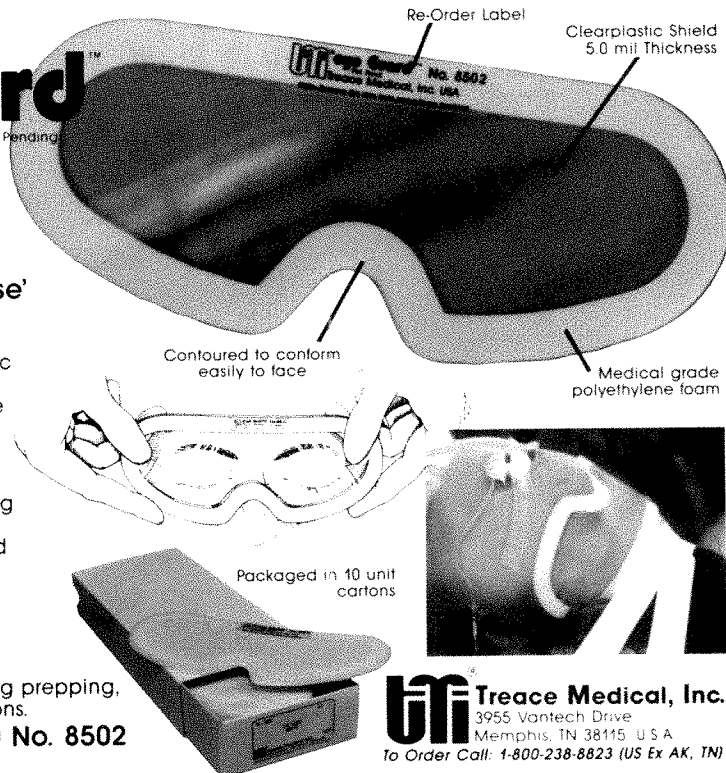
Eye Guard is a full 5.0 mil thick clear plastic shield, backed with a soft medical grade foam and non-irritating adhesive to adhere to the face and enclose the eyes.

Eye Guard is the ideal eye protector for surgical patients, allowing visualization for patient monitoring, and when administering anesthesia with a mask, prevents anesthesia gas from contacting eyes. Eye Guard minimizes the risk of accidental eye injury when placing or moving drapes or instruments and from debris. Also, Eye Guard creates a 'greenhouse' effect, keeping the eyes moist during longer procedures.

Eye Guard is non-sterile and applied during prepping, prior to draping. Packaged in 10 unit cartons.

**Pak/10 No. 8502**

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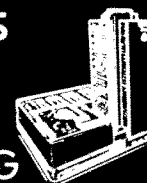


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- Resuscitation of the Newborn
- Principles of Perinatal Pharmacology
- Local Anesthetics—How Do They Work?
- Obstetrical Anesthesia and Uterine Blood Flow
- Rational Choice of Local Anesthetics for Obstetrical Anesthesia
- Choice of Vasopressors in Obstetrical Anesthesia
- Drug Interactions: Obstetric Medication and Anesthetic Agents
- Non-Obstetric Surgery in the Pregnant Patient
- Use of Epidural and Intrathecal Opiates
- Narcotic Agonists, Antagonists, and Receptors
- How to Avoid Litigation in Obstetrical Anesthesia
- Anesthetic Implications of Maternal Physiologic Changes
- Local Anesthetic Toxicity: Mechanisms, Controversies, Treatment
- Effect of Epidural Blocks on Fetal Well Being
- How to Make Spinal Anesthesia Safe

- Effect of Epidural Anesthesia on the Progress of Labor
- Continuous Infusion Epidural Blocks
- Management of the Wet Tap
- Anesthesia for Cesarean Section
- What is Our Role in Anesthetic Management of the Patient with Pregnancy-Induced Hypertension?
- Anesthetic Management of the Asthmatic Obstetric Patient
- Contending with Amniotic Fluid Embolism
- What is a "Test Dose" and Do You Need a CV Marker?
- Protection of the Fetus From Hypoxemia
- Anesthesia for Normal Delivery

#### For Information Contact:

Department of Anesthesiology, Illinois Masonic Medical Center, 836 W. Wellington, Chicago, Illinois.  
Telephone: 312/883-7035/7041. The courses are approved for 20 hours each, Category I.



# CAPNOGRAPHY SYSTEMS HAVE HAD A LOT OF PROBLEMS...

Anesthetic agents  
or contaminated  
gases exhausted  
into room

Moisture and  
Humidity leading  
to clogging

Contamination

Mucus Plugging

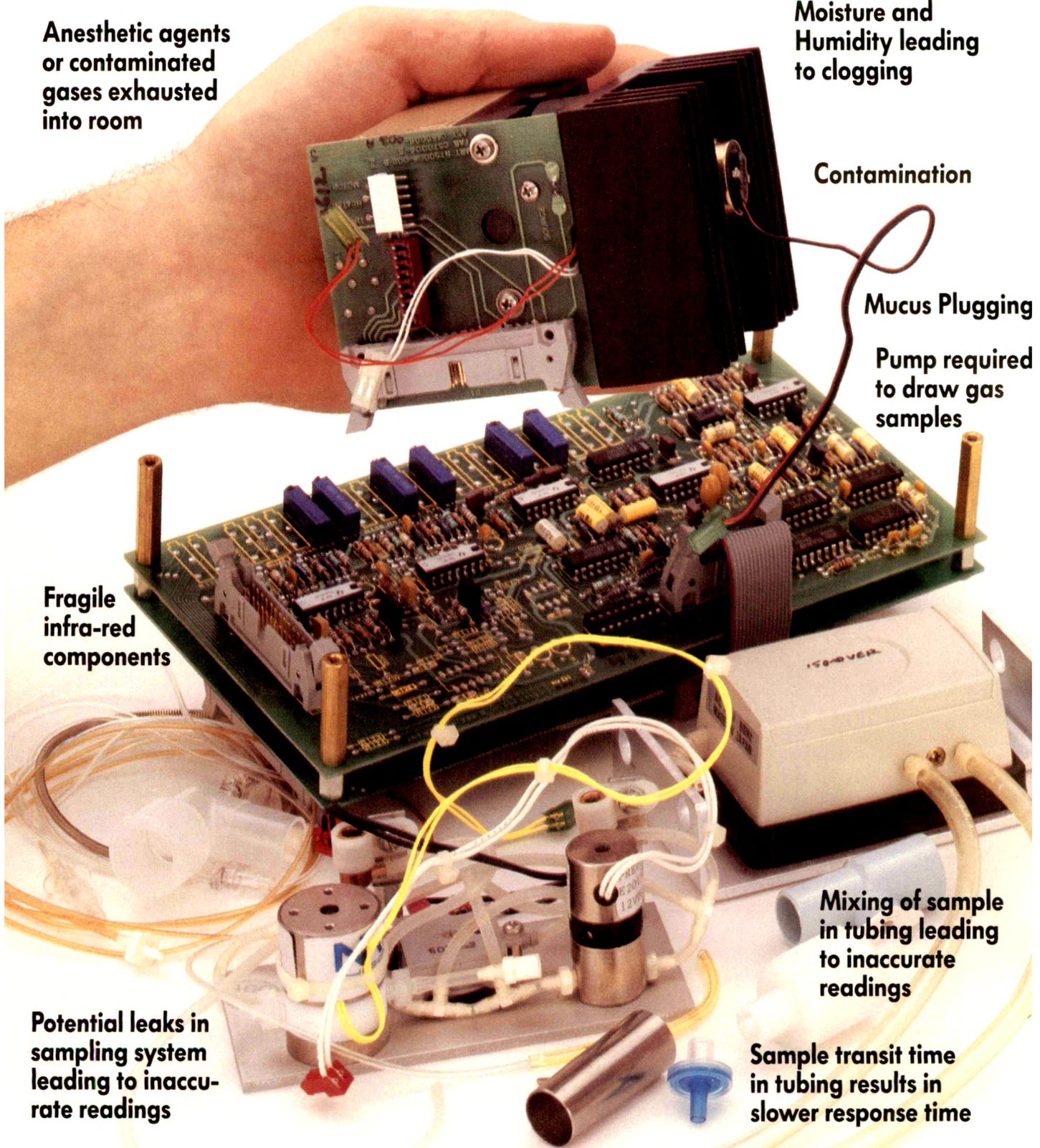
Pump required  
to draw gas  
samples

Fragile  
infra-red  
components

Potential leaks in  
sampling system  
leading to inaccurate  
readings

Mixing of sample  
in tubing leading  
to inaccurate  
readings

Sample transit time  
in tubing results in  
slower response time



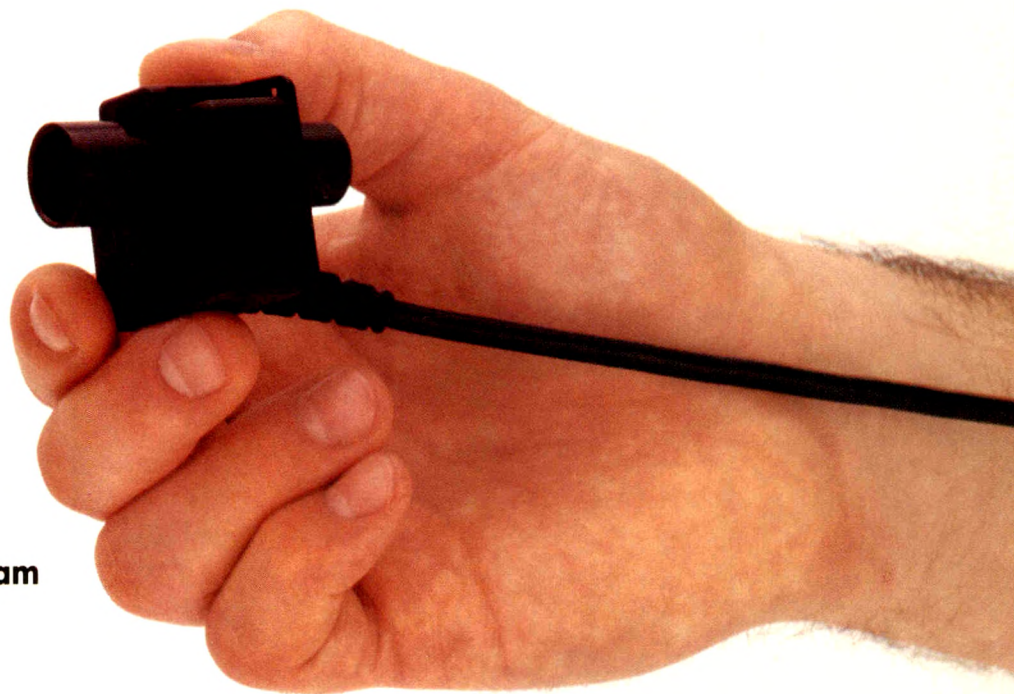


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AN OPTIMAL OPIOID  
ANESTHETIC FOR**

# **MOMENT-TO- MOMENT CONTROL**

## **RAPID ONSET OF ACTION**

for prompt control of hemodynamic response  
to surgical stimulation\*

## **SHORT DURATION OF ANALGESIC ACTION**

permits titrating to patient response

## **PROMPT RECOVERY**

in short-stay procedures†

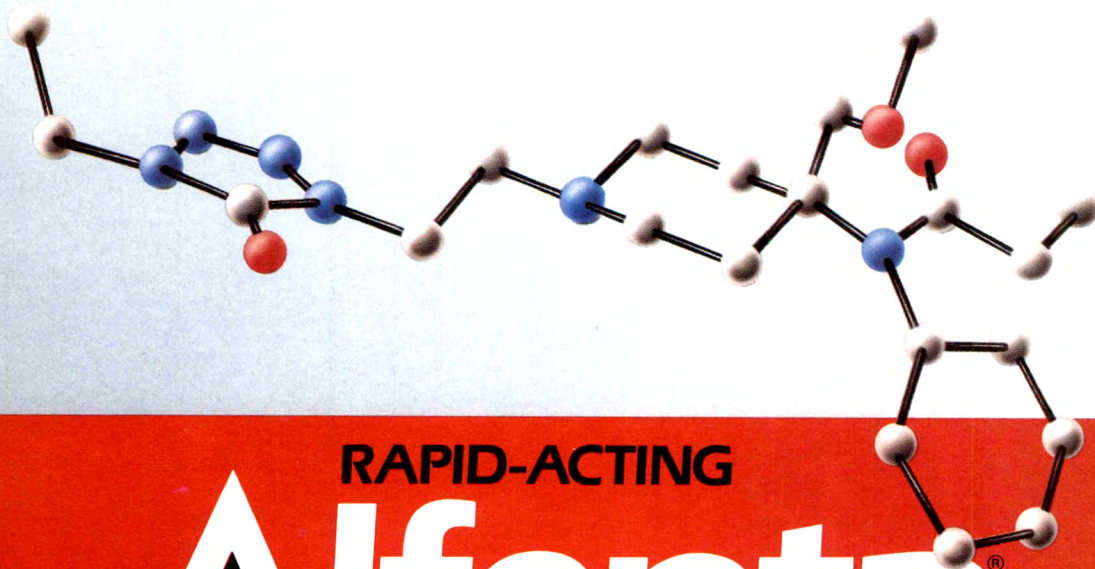
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**RAPID-ACTING**

# Alfenta<sup>®</sup>

(alfentanil HCl) Injection **Ⓜ**

**A PHARMACOKINETIC PROFILE  
THAT PERMITS FLEXIBILITY OF  
DOSING TECHNIQUE**

**BOLUS/INCREMENTAL  
ADMINISTRATION**

for short procedures lasting up to 30 minutes  
in spontaneously breathing patients, or for procedures  
lasting 30 to 60 minutes in intubated patients

**CONTINUOUS  
INFUSION**

for procedures lasting more than 45 minutes  
in intubated patients

\*As with other opioids, hypotension and bradycardia have been reported.

†As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

See following page for brief summary of Prescribing Information.



# Alfenta®

(alfentanil HCl) Injection 

## AN OPTIMAL OPIOID ANESTHETIC FOR MOMENT-TO-MOMENT CONTROL

### BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION, OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

#### CAUTION: Federal Law Prohibits Dispensing Without Prescription

**DESCRIPTION:** ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

**CONTRAINDICATIONS:** ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS:** ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

**PRECAUTIONS:** DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

**General:** The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction.

Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO<sub>2</sub> stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO<sub>2</sub>. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

**Head Injuries:** ALFENTA may obscure the clinical course of patients with head injuries.

**Impaired Respiration:** ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

**Impaired Hepatic or Renal Function:** In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

**Drug Interactions:** Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

**Pregnancy Category C:** ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

**Nursing Mothers:** In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

**Pediatric Use:** Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

**ADVERSE REACTIONS:** The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and non-disturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N=785) %	Fentanyl (N=243) %	Thiopental Sodium (N=66) %	Enflurane (N=55) %	Halothane (N=18) %	Saline Placebo* (N=18) %
<b>Gastrointestinal</b>						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
<b>Cardiovascular</b>						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
<b>Musculoskeletal</b>						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
<b>Respiratory</b>						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
<b>CNS</b>						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

\*From two clinical trials, one involving supplemented balanced barbiturate / nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

**DRUG ABUSE AND DEPENDENCE:** ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

**OVERDOSAGE:** Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD<sub>50</sub> of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

**DOSEAGE AND ADMINISTRATION:** The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

Manufactured by Taylor Pharmacal Co. for



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PHARMACEUTICA

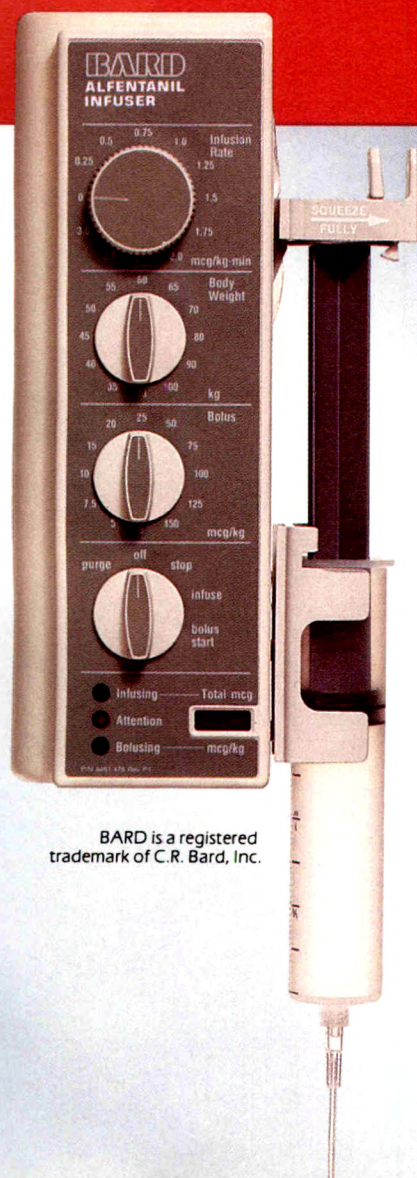
Janssen Pharmaceutica Inc.  
Piscataway, NJ 08854

U.S. Patent No. 4,167,574  
March 1987 49-7619901-M



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## MOMENT-TO- MOMENT CONTROL



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### DEDICATED PUMP FOR ALFENTANIL DELIVERY

Designed specifically for accurate administration of alfentanil

### ELIMINATES TIME-CONSUMING CALCULATIONS

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Convenient rotary switches provide optimal flexibility for bolus or infusion doses

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See preceding page for brief summary of Prescribing Information for ALFENTA® (alfentanil HCl) Injection  $\text{C}$ .



# IARS MEMBERSHIP

## FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

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**MEMBERSHIP:** Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

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*Annual Dues for Members and Associate Members:* \$60.00 U.S.; \$77.00 foreign.

These memberships are entered on a calendar year basis only.

**EDUCATIONAL MEMBERSHIP:** Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

*Annual Dues for Educational Members:* One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

---

International Anesthesia Research Society  
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

Please send me \_\_\_\_\_ application(s) for: Membership (\_\_\_\_\_)  
Associate Membership (\_\_\_\_\_)  
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# A little monitor with a lot of muscle.



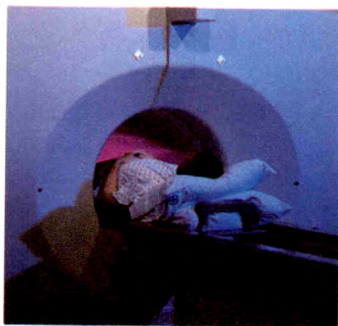
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Here at last is a surgical vital signs monitor so advanced that it integrates the most sophisticated technology into a compact, cost-effective work station. A monitor so powerful and efficient that machines twice its size don't have half the capabilities.

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# The Anesthesiology Boards Review Course

**\*Any Six Days**

**April 12 - 20, 1988 — San Francisco**

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**Now, your only BOARD REVIEW just before Oral Exams  
is also an excellent update in practice and preview for Written Exams**

## OBJECTIVES

- Improve basic and clinical knowledge in anesthesiology
- Assist residents and fellows in organizing study
- Prepare board candidates to take board examinations
- Provide practicing anesthesiologists with a review and update

## METHODS

- HOME STUDY MATERIALS with a syllabus of questions and answers — and assignments
- SEMINAR with projection slides and syllabus
- PRACTICE EXAMS with oral and written parts

\*April 12-17 and Oct. 18-23 (live). April 18-20 and Oct. 24-26 (video replays). Any six consecutive days will complete the course.

*"The faculty was outstanding. The most pleasant thing was learning a tremendous amount, not only from world-famous authorities but from people who are relatively unknown as well."*

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Respiratory Physiology  
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Endocrine Physiology  
Thermoregulation

## FUNDAMENTAL PRACTICE

Preop Evaluation & Preparation  
Positioning and Monitoring  
Airway Management  
Fluid, Electrolytes, & Blood  
Cardiopulmonary Disease  
Hepatorenal & Metabolic Disease  
Recovery Room

## PHARMACOLOGY

Pharmacokinetics  
Inhalation Anesthetics  
Intravenous Anesthetics  
Muscle Relaxants  
Autonomic Drugs  
Cardiac, Diuretic & CNS Drugs  
Drug Interaction and Genetics

## REGIONAL ANESTHESIA

Neuroanatomy  
Local Anesthetics  
Autonomic Blocks  
Spinal and Epidural Blocks  
Caudal and Peripheral Blocks  
Intravenous Nerve Blocks  
Complications & Legal Medicine

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**GOALS AND LOCATION:** The course will be held in the San Francisco Bay Area and the Tampa Bay Area as regional reviews for both written and oral exam. Home-study questions are sent upon registration. Your best value is to repeat the seminar for \$315 or \$90 the week before and in the same city as the oral exam. Topics and faculty are upgraded for each program. It is also an update for practicing anesthesiologists. Meetings will be in the best combinations of luxury hotels and bargain rates. Our previous programs at Hiltons, Hyatts, Marriott, Adam's Mark, and Meridian have been at or below \$70 single and \$84 double.

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*"...the most education for the money."*

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- Add 10% to payment after Mar. 15, 1988.
- Attendees not in course hotel add \$8/day.
- \$50.00 will reserve your position.
- Most home study materials will be mailed after half the registration fee is received.
- Additional materials will be received after completion of home study assignment.

*"...home study material was extremely helpful."*

**CANCELLATIONS:** Refunds subject to \$50 fee, will be made until the seminar begins.

- Cancellations after mailing most home study material will require retention of half of the fee.

*"...remarkably complete and pleasant."*

## INFORMATION:

Joseph H. Selliken, Jr., M.D.  
THE OSLER INSTITUTE  
1094 Dawn Lane, Terre Haute, IN 47802  
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*\* Comments by past Osler participants.*

## Limited Enrollment: ANESTHESIOLOGY BOARDS REVIEW REGISTRATION

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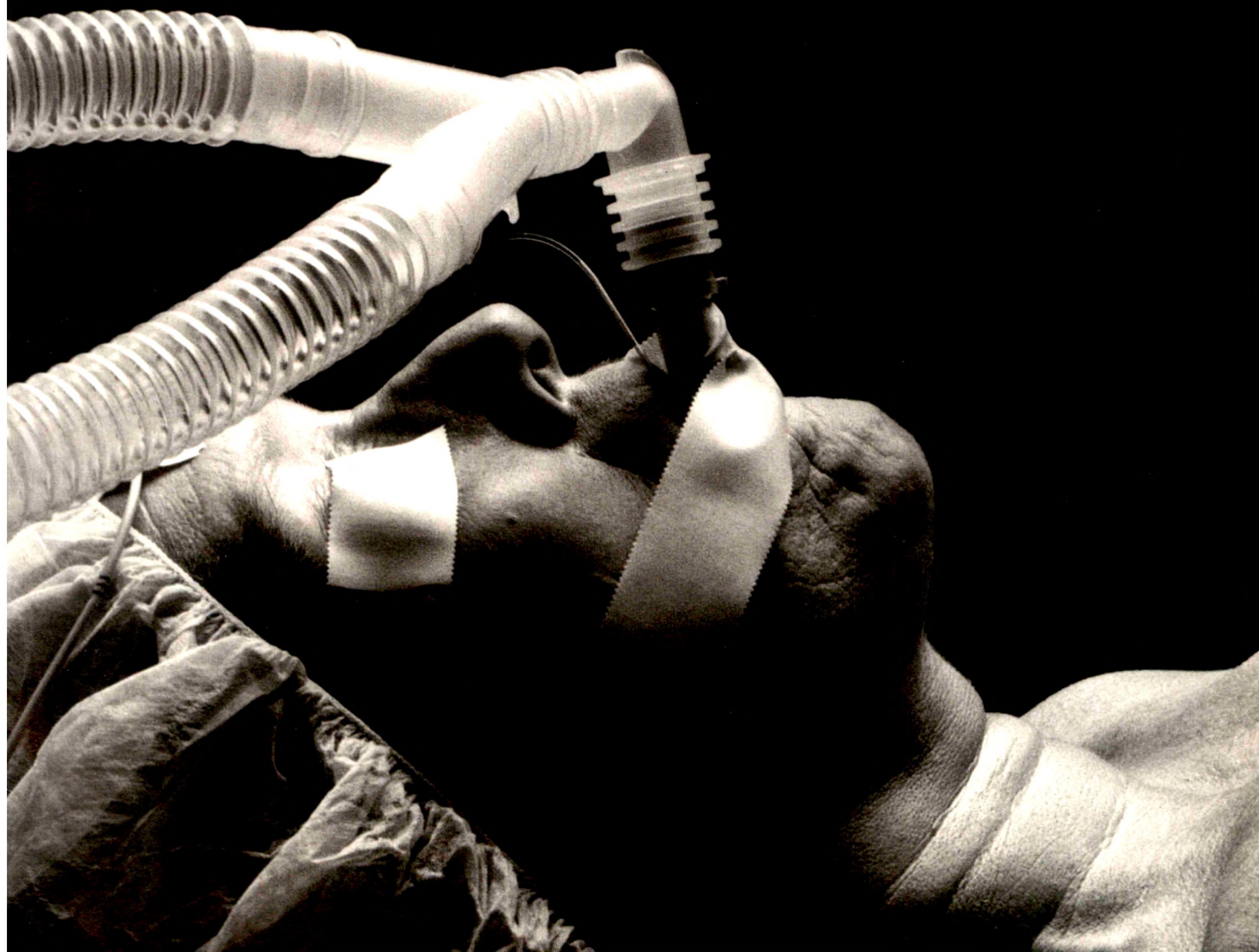
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## Mail today to:

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P.O. Box 2218  
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- For: ☐ April 12-20, 1988  
☐ October 18-26, 1988
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- ☐ Please send more information







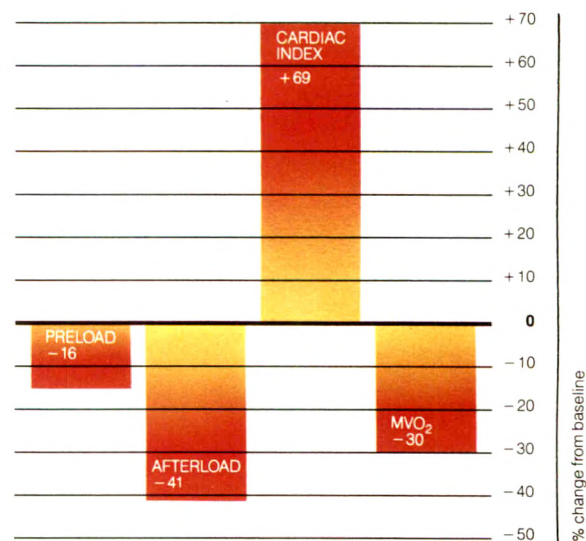
# Dual action INOCOR<sup>®</sup> I.V. (AMRINONE) Inotropic plus vasodilating action in a single drug.

Two-in-one action can improve hemodynamic response after cardiac surgery.

In patients with congestive heart failure due to coronary artery disease, INOCOR I.V. increases CI and decreases preload and afterload without increasing  $MVO_2$  or significantly increasing risk of arrhythmias.

*INOCOR I.V. is "...an extremely useful tool....I have been using amrinone...[for] inotropic support to wean patients from cardiopulmonary bypass and as a means of increasing [CI] in the post-bypass period."*\*

**Roberta Hines, M.D.**  
Yale University School of Medicine  
Yale University Hospital



†n = 8. Amrinone was infused at 2.5 mg/kg over 1 hour. Adapted from Benotti et al.<sup>1</sup>

Please see last page for important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations.

\*Interview on file, Winthrop Pharmaceuticals.

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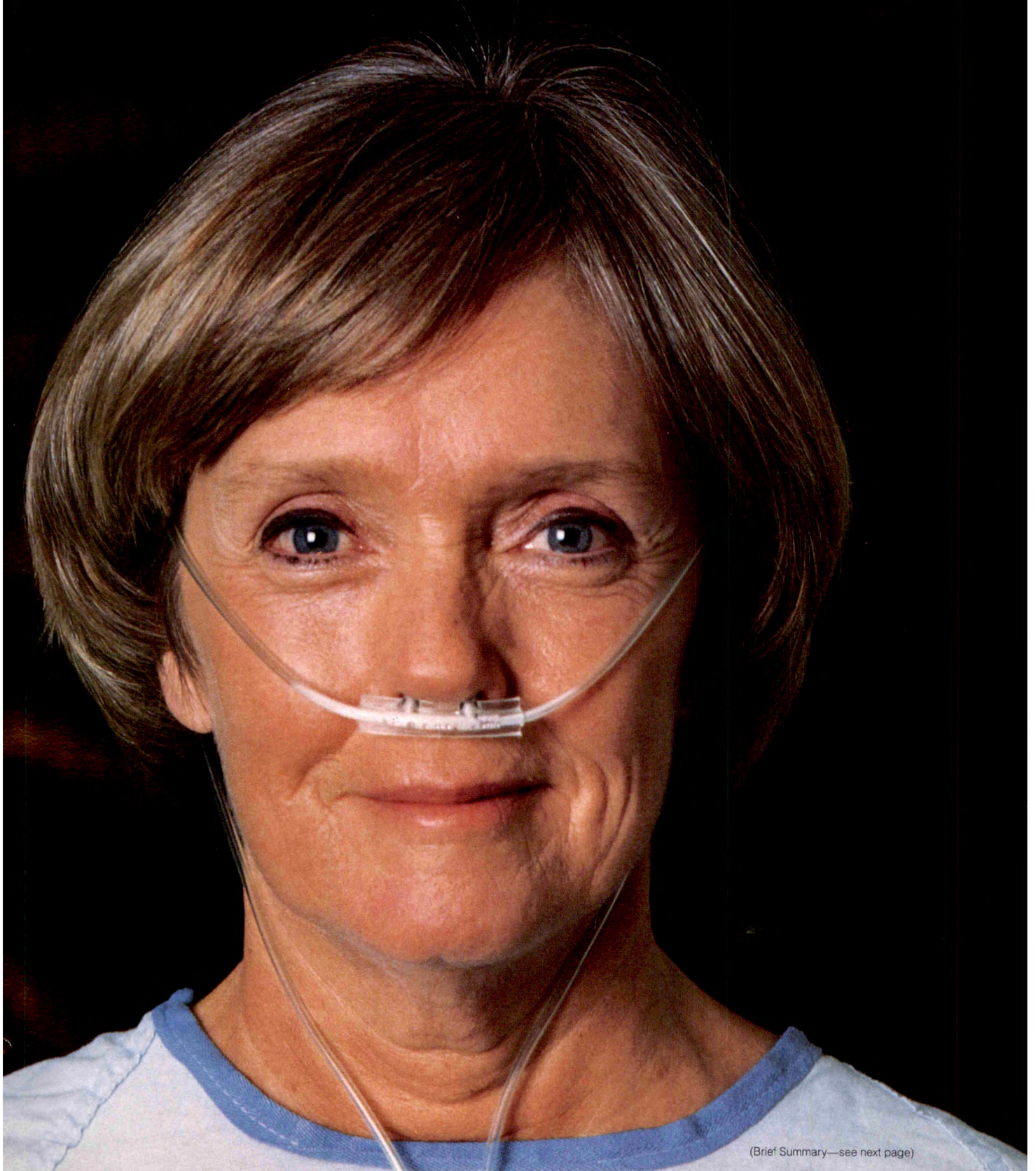
State-of-the-heart

**Inocor<sup>®</sup> I.V.**  
(AMRINONE)

Dual-acting therapy,  
instead of catecholamines



# State-of-the-heart therapy.



(Brief Summary—see next page)



# INOCOR I.V.

## Two-in-one dual inotropic and vasodilator action provides improved therapy for the cardiac surgery patient.

- Unlike catecholamines, INOCOR does not increase  $MVO_2$  and can be used in ischemic patients with heart failure.
- Unlike catecholamines, INOCOR does not act on the beta receptors—may be effectively used in patients on beta blockers.
- Unlike catecholamines, INOCOR does not significantly increase risk of arrhythmias (see Precautions).
- INOCOR has not been shown to interact with anesthetic agents.

Please consult full product information before prescribing. A summary follows. INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

**INDICATIONS AND USAGE** (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

**CONTRAINDICATIONS** INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

**PRECAUTIONS** *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

**LABORATORY TESTS** *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

**DRUG INTERACTIONS** In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate

injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol, hydralazine, prazosin, isosorbide dinitrate, nitroglycerine, chlorothalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

**USE IN ACUTE MYOCARDIAL INFARCTION** INOCOR is not recommended for use in acute myocardial infarction.

**USE IN CHILDREN** Safety and effectiveness in children have not been established.

**USE IN PREGNANCY** *Pregnancy category C:* In New Zealand white rabbits, amrinone has been shown to produce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**USE IN NURSING MOTHERS** Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

**ADVERSE REACTIONS** *Thrombocytopenia:* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm<sup>3</sup> in 2.4% of patients.

*Gastrointestinal effects:* Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

*Cardiovascular effects:* Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

*Hepatic toxicity:* In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

*Hypersensitivity:* There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case), myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case), and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of

therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

*General:* Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

**OVERDOSAGE** Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

**MANAGEMENT OF ADVERSE REACTIONS** *Platelet count reductions* Asymptomatic platelet count reduction (to less than 150,000/mm<sup>3</sup>) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm<sup>3</sup> occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

*Gastrointestinal side effects:* While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

*Hepatic toxicity:* In clinical experience to date with IV administration, hepatic toxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations.

**HOW SUPPLIED** Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection.

1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.



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# Intravenous Diltiazem Worsens Regional Function in Compromised Myocardium

Bruce J. Leone, MD, Daniel M. Philbin, MD, Jean-Jacques Lehot, MD, Mark Wilkins, Pierre Foëx, MD, Dphil, and W. Allen Ryder

LEONE BJ, PHILBIN DM, LEHOT J-J, WILKINS M, FOËX P, RYDER WA. Intravenous diltiazem worsens regional function in compromised myocardium. *Anesth Analg* 1988;67:205-10.

*The effect of intravenous diltiazem on regional myocardial function was assessed in a canine model of critical constriction of the left anterior descending coronary artery (LAD). Maintenance anesthesia with fentanyl ( $1.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ), 60% inspired nitrous oxide, and 0.7% inspired halothane resulted in regional dysfunction, measured as postsystolic shortening ( $20.6 \pm 10.7\%$ ), which was significantly worsened after  $0.1 \text{ mg/kg}$  ( $48.7 \pm 12.5\%$ ,  $P < 0.05$ ) and after  $0.2 \text{ mg/kg}$  ( $68.8 \pm 11.7\%$ ,  $P < 0.05$ ) intravenous diltiazem. Systolic shortening in the compromised LAD territory was substantially depressed after  $0.1$*

*mg/kg diltiazem ( $8.2 \pm 0.6\%$  to  $5.3 \pm 1.3\%$ ,  $P < 0.05$ ) and was essentially abolished after  $0.2 \text{ mg/kg}$  diltiazem ( $8.2 \pm 0.6\%$  to  $0.7 \pm 2.3\%$ ,  $P < 0.05$ ). At the higher dose of diltiazem, cardiac output was substantially decreased ( $1.37 \pm 0.23 \text{ L/min}$  to  $0.88 \pm 0.30 \text{ L/min}$ ,  $P < 0.05$ ) and LV  $\text{dP/dt}_{\text{max}}$  significantly depressed ( $1090 \pm 90 \text{ mm Hg/sec}$  to  $744 \pm 80 \text{ mm Hg/sec}$ ,  $P < 0.05$ ). These results demonstrate significant depression of regional systolic shortening and substantial worsening of regional dysfunction in myocardium with a compromised blood supply, in association with significant depression of left ventricular performance, with intravenous diltiazem administration during anesthesia.*

**Key Words:** HEART, MYOCARDIAL FUNCTION—ischemia. IONS, CALCIUM ANTAGONISTS—diltiazem. PHARMACOLOGY—diltiazem.

Numerous recommendations for the treatment of perioperative myocardial ischemia have been made. These recommendations are in part based on experimental laboratory investigations of reduction of myocardial infarct size. Beta-blockers, nitrates, and volatile anesthetics have all been shown to reduce myocardial infarct size (1-3). The newest class of antianginal agents, the calcium antagonists, not only decrease myocardial oxygen demand by reducing contractility and afterload but also relieve coronary artery vasospasm (4). Recent evidence of the preservation of myocardial function and metabolic activity after reperfusion of ischemic myocardium suggests that calcium antagonists also protect myocellular mechanisms from ischemic damage (5,6).

Recent investigations in our laboratory have shown that verapamil in combination with halothane causes regional myocardial dysfunction (7,8). This dysfunction, in the form of continued myocardial

segment shortening after the end of systole (postsystolic shortening), occurred despite the absence of any coronary inflow obstruction. However, this drug-induced dysfunction does not preclude beneficial effects of calcium antagonists during ischemia. We wondered whether calcium antagonism with diltiazem would reverse regional dysfunction in compromised myocardium during fentanyl-nitrous oxide-halothane anesthesia.

## Methods

The methods employed in this study conform to the Animals (Scientific Procedures) Act of 1986 (U.K.). Six mongrel dogs (weight 17-33 kg) were premedicated with morphine sulfate ( $0.1 \text{ mg/kg}$ ), anesthesia was induced with thiopental ( $4-6 \text{ mg/kg}$ ), and the trachea intubated. Positive pressure ventilation at 12 breaths/min was begun with 40%  $\text{O}_2$  in nitrogen, and the dogs were placed in the right lateral decubitus position. Anesthesia was maintained with halothane, 1.25-1.5% inspired, during the surgical preparation.

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End-tidal carbon dioxide concentration was continuously measured by infrared analysis, and ventilation was adjusted to maintain  $\text{CO}_2$  between 4.5–5.5%. Electrocardiographic leads were placed to allow calculation of heart rate and continuous monitoring of lead II of the ECG throughout the experiment.

An 8F (2.76-mm outside diameter) cannula was threaded via the femoral vein into the inferior vena cava, and a continuous intravenous infusion of Hartmann's solution ( $4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ) was begun. A common carotid artery was exposed via a neck incision, and a stiff 8F (2.76-mm outside diameter) cannula was advanced to within 1 cm of the aortic valve. This cannula was secured in place and attached to a Druck (Druck Ltd., Groby, Leicester, U.K.) pressure transducer for withdrawal of arterial blood samples and measurement of systemic arterial pressures.

A left thoracotomy was performed and the fourth and fifth ribs excised. The aortic root was dissected free of its fat pad, and an appropriately-sized electromagnetic flow probe (Transflow 601, Skalar Medical, Delft, Holland) was placed around the aortic root. A stiff 8F (2.76-mm outside diameter) cannula was inserted into the left ventricle via a stab wound in the apical dimple; this cannula was attached to a Druck pressure transducer for measurement of left ventricular (LV) pressure and its first derivative (LV  $\text{dP/dt}$ ). A cannula was placed via the right ventricular outflow tract into the pulmonary artery. The heart was then suspended in a pericardial cradle.

A small length of the left anterior descending coronary artery (LAD) proximal to its second diagonal branch was dissected free and a 2-mm electromagnetic flow probe (Transflow 601, Skalar Medical, Delft, Holland) placed around the artery. An occluding snare and a 3-0 Dacron suture also encircled the LAD. The 3-0 Dacron suture was attached to a micrometer-controlled spring-suspended snare for use in establishing critical LAD constriction (see later). Two pairs of piezoelectric crystals were placed in the LAD- and left circumflex coronary artery (LC)-supplied subendocardium. These crystals were used for myocardial segment length determinations, the techniques of which have been previously described (2,9,10). Briefly, as the speed of ultrasound through myocardium is constant at  $1.56 \text{ mm}/\mu\text{s}$ , measurement of the ultrasonic transit time between crystals allows calculation of the distance separating the crystals.

### Protocol

After completion of the surgical preparation, halothane was discontinued and a loading dose of fen-

tanyl ( $100 \mu\text{g}/\text{kg}$ ) followed by a constant infusion of fentanyl ( $1.5 \mu\text{g} \cdot \mu\text{g}^{-1} \cdot \text{hr}^{-1}$ ) was administered. This was preceded by intramuscular atropine ( $400 \mu\text{g}$ ) to avoid excessive narcotic-induced bradycardia. A 1-hour stabilization period then ensued, during which instruments were calibrated and measurements of left ventricular end-diastolic pressure (LVEDP) and arterial pH and blood gas tensions were made. Dextran 70 (average molecular weight 70,000 daltons) and bicarbonate were administered as appropriate to maintain pH between 7.43 and 7.45 and LVEDP  $> 5 \text{ mm Hg}$ .

Critical constriction was then imposed on the LAD by gradual tightening of the micrometer-controlled snare until no hyperemic response to a 10-second coronary occlusion was evident, yet no regional dysfunction (i.e., postsystolic shortening) was observed (11). Confirmation of correct placement of the pairs of crystals and the lack of significant collateralization was obtained by observing hypokinesia and dyskinesia in the signals from the LAD crystals, and not the LC crystals, during a 10-second LAD occlusion. Nitrous oxide, 60% inspired, was added to the anesthetic by abruptly replacing nitrogen in the fresh gas flow. Halothane (0.7% inspired) was then administered; with this anesthetic circuit and vaporizer, this concentration corresponds to a steady state end-tidal halothane concentration of  $0.54\% \pm 0.01$  after 20 minutes as measured by refractometry and infrared analysis. A baseline set of data were recorded. Intravenous diltiazem  $0.1 \text{ mg}/\text{kg}$  was then administered and recordings taken after 10 minutes. A second dose of  $0.1 \text{ mg}/\text{kg}$  was injected, and observations were recorded after 10 minutes.

During the course of the experimental procedure, indocyanine green was injected into the pulmonary artery cannula and cardiac output dye dilution curves were obtained by densitometric analysis. The aortic flowmeter was thus calibrated and from this calibration all flow-derived parameters were obtained. At the conclusion of the experimental protocol the LAD was cannulated and calibration of the LAD flow probe performed by injecting 5-ml aliquots of blood through the cannula. After calibration, 5 ml of Evans blue was injected through the LAD cannula. The resulting area of stained myocardium, representing the territory supplied by the LAD, was separated from nonstained myocardium. The atria were removed and the stained ventricular myocardial fragments weighed, thus enabling LAD flow measurements to be normalized as  $\text{ml} \cdot \text{min}^{-1} \cdot 100\text{g}^{-1}$  of myocardium.

Aortic and left ventricular pressures were recorded, as well as aortic blood flow, stroke volume



Table 1. Global Hemodynamics and End-Diastolic Lengths\*

	Baseline	Diltiazem	
		0.1 mg/kg	0.2 mg/kg
HR (beats/min)	106 ± 8	112 ± 11	99 ± 10
SAP (mm Hg)	97 ± 7	85 ± 5	74 ± 8
DAP (mm Hg)	64 ± 7	55 ± 6	48 ± 7
LVEDP (mm Hg)	6.8 ± 1.2	7.8 ± 1.2	11.3 ± 1.6
LV dP/dt <sub>max</sub> (mm Hg/sec)	1090 ± 90	930 ± 60	744 ± 80†
CO (L/min)	1.37 ± 0.23	1.27 ± 0.27	0.88 ± 0.30†
CBF (ml·100g <sup>-1</sup> ·min <sup>-1</sup> )	38.6 ± 10.5	32.4 ± 15.6	23.0 ± 9.0
EDL-LAD (mm, normalized)‡	10.0 ± 0.25	10.0 ± 0.3	10.1 ± 0.3
EDL-LC (mm, normalized)‡	10.1 ± 0.3	10.2 ± 0.3	10.4 ± 0.4

\*Data are mean ± SEM.

† $P < 0.05$  by two-way analysis of variance and Duncan's multiple range test.‡Lengths normalized to a precritical constriction end-diastolic length of 10.0 mm. Abbreviations: HR, heart rate; SAP, systemic arterial pressure, systolic; DAP, systemic arterial pressure, diastolic; LVEDP, left ventricular end-diastolic pressure; LV dP/dt<sub>max</sub>, maximum positive deflection of the first derivative of left ventricular pressure; CO, cardiac output; CBF, coronary blood flow; EDL-LAD, end-diastolic length, LAD region; EDL-LC, end-diastolic length, LC region.

(obtained by integration of aortic flow) and LV dP/dt. The signals were recorded in analog form on a Mingograf 81 eight-channel recorder (Elema Schöander, Stockholm, Solna, Sweden). Length measurement involved calculations of end-diastolic length (EDL) and end-systolic length (ESL). For determination of these lengths, the timing of end-diastole was taken as the first positive deflection of LV dP/dt. End-systole was defined as the point at which aortic valve closure occurred, that is, the point when aortic blood flow returned to zero. All length recordings were taken at a paper speed of 250 mm/sec for precise determinations of the end of diastole and systole.

### Computation

The data were digitized manually from hard copy recordings. These data were then analyzed on a VAX computer utilizing SAS, a commercially available statistical analysis system (SAS, Inc., Cary, N.C.).

Mean arterial pressure (MAP) was calculated from the systolic and diastolic systemic arterial pressures (SAP, DAP). Coronary perfusion pressure (CPP) was calculated in the conventional fashion as the difference between DAP and left ventricular end-diastolic pressure (LVEDP). The maximum positive deflection of LV dP/dt (LV dP/dt<sub>max</sub>) was also noted. Cardiac output (CO) was calculated from the heart rate and stroke volume.

Regional function was examined by calculating systolic shortening and postsystolic shortening. Systolic shortening (SS) was defined as EDL minus ESL, and expressed as a percentage of EDL to compensate for preload-induced changes of performance. Post-

systolic shortening (PSS) was defined as the difference between ESL and the resultant minimum segment length attained during diastole. This was expressed as a percentage of the total segment shortening to compensate for changes in inotropy.

Data were analyzed for statistical significance using two-way analysis of variance and Duncan's multiple range test when appropriate. Some parameters, notably PSS and LAD coronary blood flow (CBF), exhibited skewed distribution and thus were analyzed by the nonparametric Friedman two-way analysis of variance and, when appropriate, sign test. In all cases,  $P < 0.05$  was considered statistically significant.

### Results

Global hemodynamic data are presented in Table 1. Heart rate (HR) showed no change from baseline after either injection of diltiazem, and all of the dogs continued to have sinus rhythm. LV dP/dt<sub>max</sub> and CO declined significantly after the second dose of diltiazem. Other hemodynamic variables decreased, but none achieved statistical significance.

Regional function data revealed significant depression of LAD (compromised region) SS with each diltiazem dose. From a baseline value of  $8.2\% \pm 0.6$ , SS decreased significantly to  $5.3\% \pm 1.3$  after 0.1 mg/kg of diltiazem and to  $0.7\% \pm 2.3$  ( $P < 0.05$  vs baseline) after 0.2 mg/kg (cumulative dose) of diltiazem. In contrast, SS in the LC (noncompromised) region was unaffected (Fig. 1).

Postsystolic shortening in the compromised LAD territory increased significantly above baseline after the first dose ( $20.6 \pm 10.7$  to  $48.7\% \pm 12.5$ ) and after



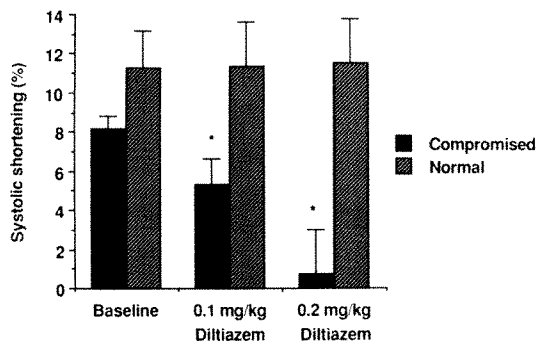


Figure 1. Systolic shortening in the critically constricted LAD-supplied territory and the unconstricted LC-supplied territory before calcium channel blockade and after 0.1 mg/kg and 0.2 mg/kg (cumulative doses) intravenous diltiazem. Baseline condition refers to maintenance anesthesia consisting of  $1.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  continuous infusion of fentanyl, 60% inspired nitrous oxide, and 0.7% inspired halothane. \* $P < 0.05$  vs baseline by Friedman two-way analysis of variance and sign test.

the second dose ( $20.6\% \pm 10.7$  to  $68.8\% \pm 11.7$ ) of intravenous diltiazem. Postsystolic shortening in the noncompromised LC region was essentially unchanged (Fig. 2).

## Discussion

Verapamil, nifedipine and diltiazem have been shown to improve angina and coronary spasm (12,13). In addition, calcium antagonists preserve regional contractile performance and myocardial cellular energy stores after global ischemia and reperfusion (5,6,14) and after transmural ischemia (15,16). Diltiazem may be preferable in clinical situations, owing to its lesser effects on conduction and contractility, as well as a decreased incidence of side effects, when compared to verapamil and nifedipine (17).

However, the combination of a volatile anesthetic and verapamil causes regional myocardial dysfunction, seen as PSS, in apical myocardium with a normal coronary blood supply (7,8,18). Postsystolic shortening is also a consistent feature of regional myocardial ischemia in both laboratory and clinical studies (19,20). Whether drug-induced PSS is the same phenomenon as that occurring during ischemia is not known, but the development of PSS with the combination of a calcium antagonists and a volatile anesthetic with normal coronary arterial supply does not preclude improvement of regional function by calcium antagonists during ischemia.

The present study utilized critical constriction of the LAD to simulate significant coronary artery disease, and significant regional dysfunction in the compromised territory occurred when 60% inspired

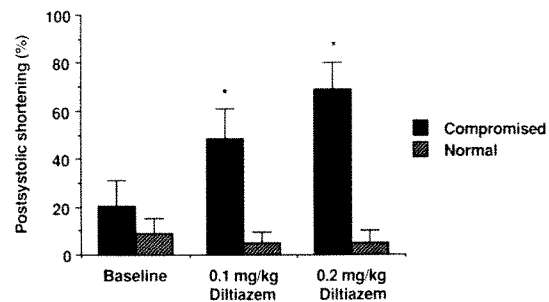


Figure 2. Postsystolic shortening in the critically constricted LAD-supplied territory and the unconstricted LC-supplied territory before calcium channel blockade and after 0.1 mg/kg and 0.2 mg/kg (cumulative doses) intravenous diltiazem. Baseline condition refers to maintenance anesthesia consisting of  $1.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  continuous fentanyl infusion, 60% inspired nitrous oxide, and 0.7% inspired halothane. \* $P < 0.05$  vs baseline by Friedman two-way analysis of variance and sign test.

nitrous oxide and 0.7% inspired halothane were added to a narcotic-based anesthetic. We then administered intravenous diltiazem so that the cumulative doses (0.1 and 0.2 mg/kg) approximated the dose (0.15 mg/kg) shown to reverse left ventricular asynergy in awake patients with coronary artery stenosis (21). Our results showed significant worsening of PSS and a substantial reduction of SS in the compromised LAD territory with both diltiazem doses. The non-compromised LC segment was apparently not affected, although no compensatory increase in function of the LC region was observed, as has been previously demonstrated with worsening LAD regional function (11) (Figs. 1 and 2). Some depression of global hemodynamics also occurred, but statistically significant decreases were only observed in LV  $\text{dP}/\text{dt}_{\text{max}}$  and CO at the higher diltiazem dose (Table 1). However, the absence of significant changes in SAP, DAP and LVEDP may reflect the small study size rather than a lack of effect.

The mechanism causing PSS, and whether drug-induced and ischemic PSS are the same phenomenon or are caused by effects on the same mechanism, is unknown. The administration of a powerful coronary vasodilator, such as adenosine or dipyridamole, can cause transmural steal and subendocardial ischemia in experimental models of coronary stenosis (22,23). Diltiazem and verapamil, both powerful coronary vasodilators (16), may possibly induce subendocardial ischemia by causing such a redistribution of transmural blood flow away from the subendocardium. Alternatively, interference with calcium release and/or reuptake by myocardial cells by calcium antagonists in combination with volatile anesthetics may result in abnormal myocardial cellular contractile function and regional dysfunction, such as that seen with halothane or isoflurane and verapamil (7,8,18).



Because of the number of different agents employed in this model, all having some effect on myocardial blood flow or contractility, it would be difficult to ascribe these changes to a specific hemodynamic effect of or drug interaction with diltiazem. However, this model was an attempt to simulate clinical situations, in which concurrent use of several anesthetic and cardiac drugs is common.

The depression of systolic shortening in the compromised LAD segment was coupled with significant depression of CO at the higher diltiazem dose. Selective depression of ischemic myocardium by verapamil has been reported, and Smith et al. (24) remarked that this depression may be beneficial to ischemic myocardium because of the resultant decrease in myocardial oxygen demand. They also noted a change in the contractile patterns of the compromised segment, similar to worsening ischemia, and commented that the beneficial effects of verapamil would only be seen if global left ventricular function was preserved. Kates et al. (25) observed depression of CO by diltiazem during halothane anesthesia in swine; however, the doses of diltiazem they employed were far in excess of those used clinically (25). The significant depression of contractile performance in the compromised myocardium and the simultaneous marked depression of global left ventricular performance seen in this study suggests caution when administering intravenous diltiazem to anesthetized patients with coronary artery disease.

In summary, the administration of intravenous diltiazem during halothane-nitrous oxide-fentanyl anesthesia resulted in marked depression of systolic shortening and worsening of regional myocardial dysfunction in myocardium supplied by a critically narrowed coronary artery. These changes in regional function were accompanied by decreases in global left ventricular performance, as measured by  $LV\ dp/dt_{max}$  and CO. The mechanism by which diltiazem depressed contraction and exacerbated dysfunction is unknown, but a drug interaction between halothane and diltiazem, resulting in transmural myocardial steal with subendocardial underperfusion or interference with calcium ion fluxes, or both, may be responsible. Although extrapolation to clinical situations is difficult, these results suggest that deleterious effects on myocardium with a compromised blood supply may occur when intravenous diltiazem is administered during anesthesia.

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## Regional Hemodynamics and Oxygen Supply During Isovolemic Hemodilution Alone and in Combination with Adenosine-Induced Controlled Hypotension

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CRYSTAL GJ, ROONEY MW, SALEM MR. Regional hemodynamics and oxygen supply during isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension. *Anesth Analg* 1988;67:211-8.

*Studies were performed in ten pentobarbital-anesthetized, open chest dogs to evaluate regional circulatory effects of isovolemic hemodilution alone, and in combination with adenosine-induced controlled hypotension. Regional blood flow measured with 15- $\mu$ m radioactive microspheres was used to calculate regional oxygen supply. Hemodilution with 5% dextran (40,000 molecular weight) reduced arterial hematocrit and oxygen content by approximately one-half and caused heterogeneous changes in regional blood flows; flow decreased in the spleen, was unchanged in the renal cortex, liver, skeletal muscle and skin, and increased in the duodenum, pancreas, brain and myocardium; however, only in the brain and myocardium were increases in flow sufficient to preserve oxygen supply. Intravenous infusion of adenosine reduced aortic pressure by 50% and*

*reduced flow in most tissues (renal cortex, pancreas, liver, spleen, skin, and brain), with the result that oxygen deficits were produced or accentuated in these organs. The magnitude of flow reductions in the renal cortex (-73%) and cerebral cortex (-37%) were noteworthy. In the myocardium, direct coronary vasodilation by adenosine caused parallel increases in blood flow and oxygen supply to levels exceeding prevailing metabolic requirements. It is concluded that 1) during isovolemic hemodilution alone, oxygen supply to the brain and myocardium is maintained at the expense of oxygen supply to less critical organs and, 2) during combined isovolemic hemodilution and adenosine-induced hypotension, oxygen is oversupplied to the myocardium but undersupplied to the brain and kidney. These latter effects suggest the need for extensive clinical monitoring of patients in whom combined isovolemic hemodilution and adenosine-induced hypotension is utilized.*

**Key Words:** ANESTHETIC TECHNIQUES, HYPOTENSIVE—adenosine. BLOOD, ANEMIA—iso-volemic.

The costs and risks involved with homologous blood transfusions have prompted the development of methods to minimize blood loss during surgery. Among these methods is drug-induced controlled hypotension. The drawbacks of the commonly used hypotensive drugs such as halothane, nitroglycerin, nitroprusside, and trimethaphan include cyanide toxicity, tachyphylaxis, rebound hypertension and ex-

cessive cerebral vasodilation (1-5). This has stimulated interest in the use of exogenous adenosine to induce controlled hypotension (1,6-8). Adenosine, a metabolic breakdown product of adenosine triphosphate, is an endogenous vasodilator that has been implicated in local regulation of coronary blood flow (9).

Intravenous infusion of adenosine causes arterial hypotension that is rapidly achieved, easily controlled, and short-lived (1,6-8). Two additional features of adenosine increase its appeal as a hypotensive drug. First, intravenous adenosine has a favorable influence on myocardial oxygen supply/demand balance because it increases coronary blood flow (myocardial oxygen supply) while at the same time decreasing myocardial oxygen demand (8). Second, adenosine does not cross the blood-brain barrier and thus has no direct effect on cerebral vascular

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smooth muscle when injected intravenously (6). Because cerebral autoregulation remains intact during adenosine-induced hypotension, cerebral blood flow remains near normal, which may be a distinct advantage during neurosurgery.

Recent reports have suggested combining controlled hypotension with isovolemic hemodilution, which is another method of blood conservation (10,11). Because the coexistence of decreased perfusion pressure and reduction in oxygen-carrying capacity of the arterial blood may risk development of tissue hypoxia, studies of regional hemodynamics are necessary before a technique of combined hypotension and hemodilution can be considered for clinical use.

Accordingly, the present study was designed to assess effects of isovolemic hemodilution alone and in combination with adenosine-induced controlled hypotension on hemodynamics and oxygen supply in regional circulations of anesthetized dogs.

## Methods

### *Experimental Preparation*

Experiments were performed on ten mongrel, heart-worm-free, conditioned dogs of either sex (weight range 21–24 kg), anesthetized with pentobarbital sodium 30 mg/kg initially, with supplementation as required to maintain a stable anesthetic state. After tracheal intubation, the dogs were ventilated by a Harvard respiratory pump with room air. Physiologic levels of arterial  $\text{Po}_2$  and  $\text{PCO}_2$  were established by adjusting the volume and rate of the respirator and by adding oxygen to the inspired gas. Arterial pH was maintained as close to 7.4 as possible. Sodium bicarbonate was administered intravenously as necessary to correct arterial base deficits.  $\text{Po}_2$ ,  $\text{PCO}_2$ , and pH of arterial blood samples were measured electrometrically (Radiometer, model ABL-1, Copenhagen, Denmark). Rectal temperature was monitored and maintained at 38°C with a heating pad.

Polyethylene cannulas were inserted 1) into the thoracic aorta via the right femoral and right brachial arteries for monitoring aortic blood pressure and for obtaining samples of arterial blood for analysis of gas tensions and, 2) into the right femoral vein for administration of supplementary anesthetic and other intravenous injections. The heart was exposed through a left thoracotomy in the fourth intercostal space. Polyethylene cannulas were placed in 1) the left atrium via the atrial appendage for monitoring left atrial pressure and for injecting radioactive microspheres, 2) the left ventricle via the left atrial append-

age and the mitral valve for measuring left ventricular pressure and, 3) the left femoral vein and right carotid artery for isovolemic exchange of whole blood with dextran solution. A noncannulating flow transducer was placed around the ascending aorta to measure cardiac output (less coronary blood flow) using an electromagnetic flowmeter (Narco Biosystems). Heparin 300 U/kg IV was administered to prevent blood coagulation in exchange circuits.

Vascular pressures were measured with Statham transducers (model P23ID) and averaged electronically. The left ventricular systolic pressure pulse was used to drive a cardiometer and it was differentiated to yield  $\text{dP/dt}_{\text{max}}$ . Blood pressures, aortic blood flow, and heart rate were recorded with a Gould recorder (model 2800S). Systemic vascular resistance (excluding coronary bed) was computed by dividing mean aortic pressure by mean aortic blood flow.

The statistical significance of differences between treatment means was tested using a randomized block analysis of variance in conjunction with the Student-Newman-Keuls test (12).  $P < 0.05$  was considered statistically significant throughout this study.

### *Measurement of Regional Blood Flow*

Regional blood flow was measured with  $15 \pm 3 \mu\text{m}$  microspheres labeled with  $\gamma$ -emitting radionuclides,  $^{141}\text{cerium}$ ,  $^{51}\text{chromium}$ ,  $^{46}\text{scandium}$ ,  $^{85}\text{strontium}$  and  $^{113}\text{tin}$  (New England Nuclear Corp.; 3M Company) (13). Before injection, microspheres were dispersed in a solution of 10% dextran and agitated in a vortex mixer and in an ultrasonic bath. Approximately  $1 \times 10^6$  microspheres were administered for each flow determination. The microspheres were flushed into the left atrium over 30 seconds with 5-ml body-temperature isotonic saline. Administration of microspheres had no detectable effect on monitored hemodynamic parameters. Beginning simultaneously with each microsphere injection, duplicate reference arterial samples were collected for 3 minutes through two cannulas of different lengths inserted into the aorta via the left femoral artery. Similar radioactivities of these duplicate reference samples verified adequate mixing of microspheres in the left ventricular output.

After the final injection of microspheres, the heart was stopped by intravenous injection of KCl, excised, and frozen to facilitate transmural sampling. Myocardial samples were obtained from the left and right ventricular free walls. The brain was removed and samples were obtained from the cerebral cortex, cerebellum, pons, medulla, and cervical spinal cord. Samples of renal cortex, pancreas, spleen, liver, du-

odenum, skin, and skeletal muscle were also obtained. Most tissue samples contained at least 400 microspheres to ensure high-precision, low-error flow measurements (14). The precision of measurements in tissues with low flows, e.g., skin, was improved by using larger samples. Each section was transferred to a tared counting tube. The tissue and reference blood samples were weighed and analyzed for radioactivity with a gamma scintillation counter equipped with a multichannel analyzer (LKB model 1282-002). Isotope separation was accomplished by standard techniques of gamma spectroscopy. Values for regional blood flow (RBF) in  $\text{ml} \cdot \text{min}^{-1} \cdot 100\text{g}^{-1}$  were calculated from the equation:

$$\text{RBF} = \text{ABF} \times (\text{MC}/\text{AC}) \times 100,$$

where ABF is the arterial reference sampling ( $\text{ml}/\text{min}$ ), MC is microsphere radioactivity ( $\text{counts} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ ) in the tissue samples, and AC is the total microsphere radioactivity ( $\text{counts}/\text{min}$ ) in the arterial reference samples. Regional vascular resistance was computed by dividing mean aortic blood pressure by regional blood flow.

Oxygen content of arterial blood samples was measured with a Lex-O<sub>2</sub>-Con (Lexington Instruments). These values were multiplied by aortic flow values to yield systemic oxygen supply and by regional blood flow values to yield regional oxygen supply.

### Experimental Protocols

Dogs were permitted to stabilize physiologically for at least 30 minutes after surgical preparation baseline measurements of regional blood flow and oxygen supply were obtained. Isovolemic hemodilution was produced by removing blood from a carotid artery at a rate of 20  $\text{ml}/\text{min}$  while replacing it with 5% dextran (molecular weight 40,000; American McGaw) at the same rate. The total volume exchanged was 45  $\text{ml}/\text{kg}$ . A second set of measurements of regional blood flow and regional oxygen supply was obtained after the preparation was permitted to stabilize for 15 minutes after completion of fluid exchange. Adenosine (60  $\text{mmol}/\text{L}$  in isotonic saline) was then infused intravenously at a rate of 81–300  $\text{mmol}/\text{min}$ , a rate sufficient to reduce mean aortic blood pressure by 50%. The rate of infusion of adenosine was held constant throughout the hypotensive period. Because a highly concentrated adenosine solution was used, low infusion rates ( $3.1 \pm 0.5 \text{ ml}/\text{min}$ ) prevented further decreases in arterial hematocrit during controlled hypo-

tension. The adenosine solution required continual heating and stirring to avoid precipitation of adenosine crystals. In all dogs measurements were obtained 15 minutes after start of adenosine infusion, and, in four of the dogs, 60 minutes after start of adenosine infusion. Replacement of blood samples withdrawn for analysis of gas tensions and radioactivity levels was performed throughout all experiments to maintain isovolemic conditions.

## Results

### Systemic Effects (Table 1)

Hemodilution caused a 52% reduction in arterial hematocrit and a proportional reduction in arterial oxygen content. An increase in aortic blood flow (+43%) blunted the decrease in systemic oxygen supply caused by this reduction in arterial oxygen content. Hemodilution reduced systemic vascular resistance (–37%), while it had no significant effect on aortic blood pressure, left atrial pressure, left ventricular  $\text{dP}/\text{dt}_{\text{max}}$ , or heart rate.

Data during hemodilution alone served as a reference for evaluating effects of intravenous infusion of adenosine. Adenosine infusion, at a rate sufficient to decrease mean aortic pressure by one-half, reduced left ventricular  $\text{dP}/\text{dt}_{\text{max}}$  (–28%), heart rate (–35%), aortic blood flow (–14%), and systemic vascular resistance (–39%). Other systemic vascular parameters were unchanged.

### Regional Effects

Hemodilution caused heterogeneous changes in regional flow in peripheral beds (Table 2), depending on changes in vascular resistance in the various organs (Table 3). Hemodilution was associated with increased flow in the pancreas (+62%) and duodenum (+53%), with reduced flow in the spleen (–31%), and without significant effect on flow in renal cortex, liver (hepatic arterial bed), skeletal muscle and skin. However, in all these beds, oxygen supply decreased (Table 4).

Hemodilution caused increases in blood flow in the brain and myocardium (Table 2) that reflected the decreases in regional vascular resistance (Table 3). These increases in blood flow to the brain and myocardium were sufficient to maintain regional oxygen supply at the baseline level (Table 4).

Adenosine-induced hypotension reduced flow in the renal cortex (–73%), pancreas (–43%), liver (–52%), spleen (–68%), and skin (–55%), while it



Table 1. Changes in Systemic Hemodynamic Parameters During Hemodilution Alone and During Combined Hemodilution and Adenosine-Induced Controlled Hypotension

	Control	Hemodilution alone	Hypotension during hemodilution
Mean aortic pressure (mm Hg)	110 ± 6	103 ± 5	51 ± 3*†
Systolic aortic pressure (mm Hg)	125 ± 6	124 ± 4	77 ± 3*†
Diastolic aortic pressure (mm Hg)	101 ± 6	92 ± 5	42 ± 3*†
Mean left atrial pressure (mm Hg)	4.3 ± 0.5	6.1 ± 0.7	5.7 ± 1.0
Left ventricular dP/dtmax (mm Hg/sec)	1700 ± 93	1815 ± 137	1315 ± 137*†
Heart rate (beats/min)	163 ± 11	160 ± 9	104 ± 4*†
Aortic blood flow (ml/min)	1182 ± 135	1691 ± 187*	1453 ± 175*†
Systemic vascular resistance (excluding coronary bed) (mm Hg·ml <sup>-1</sup> ·min <sup>-1</sup> )	0.106 ± 0.014	0.067 ± 0.007*	0.041 ± 0.007*†
Arterial hematocrit (%)	44.9 ± 2.4	21.7 ± 1.6*	22.0 ± 1.9*
Arterial oxygen content (vol. %)	21.2 ± 1.2	9.6 ± 0.8*	10.0 ± 1.0*
Systemic oxygen supply (ml/min)	251.7 ± 34.5	163.5 ± 26.6*	131.6 ± 17.1*

Values are mean ± SE in ten dogs.

\*P &lt; 0.05 from control.

†P &lt; 0.05 from hemodilution alone.

Table 2. Changes in Blood Flows (ml·min<sup>-1</sup>·100g<sup>-1</sup>) in Regional Vascular Beds During Isovolemic Hemodilution Alone and During Combined Isovolemic Hemodilution and Adenosine-Induced Controlled Hypotension

	Control	Hemodilution alone	Hypotension during hemodilution
Renal cortex	491 ± 41	463 ± 51	123 ± 32*†
Pancreas	13 ± 1	21 ± 2*	12 ± 1†
Duodenum	34 ± 2	52 ± 3*	49 ± 7*
Liver (hepatic bed)	17 ± 6	21 ± 3	10 ± 2†
Spleen	215 ± 34	149 ± 27*	48 ± 12*†
Skeletal muscle	4.4 ± 0.6	4.8 ± 1.0	2.9 ± 0.4
Skin	2.9 ± 0.4	3.3 ± 0.7	1.5 ± 0.2*†
Brain			
Cerebral cortex	29 ± 3	70 ± 7*	44 ± 5*†
Cerebellum	31 ± 2	55 ± 4*	44 ± 4*†
Pons	23 ± 2	44 ± 4*	34 ± 3*†
Medulla	24 ± 2	43 ± 5*	38 ± 3*
Spinal cord	13 ± 2	23 ± 3*	20 ± 2*
Myocardium			
Left ventricle	61 ± 4	140 ± 12*	230 ± 27*†
Right ventricle	40 ± 4	82 ± 6*	251 ± 20*†

Values are mean ± SE in ten dogs.

\*P &lt; 0.05 from control.

†P &lt; 0.05 from hemodilution alone.

had no significant effect on flow in duodenum and skeletal muscle. Increases in vascular resistance augmented the decreases in flow in the renal cortex (+238%) and spleen (+50%). Adenosine infusion lowered oxygen supply in the renal cortex (-74%), pancreas (-26%), and spleen (-66%), but had no significant effect on oxygen supply in the duodenum, liver, skeletal muscle and skin.

Even though regional vascular resistance decreased throughout the brain during adenosine-induced hypotension, these decreases were sufficient

Table 3. Changes in Vascular Resistance (mm Hg·ml·min<sup>-1</sup>·100g<sup>-1</sup>) in Regional Vascular Beds During Isovolemic Hemodilution Alone and During Combined Isovolemic Hemodilution and Adenosine-Induced Controlled Hypotension

	Control	Hemodilution alone	Hypotension during hemodilution
Renal cortex	0.24 ± 0.02	0.24 ± 0.02	0.81 ± 0.22*†
Pancreas	8.63 ± 0.77	5.76 ± 1.13*	4.27 ± 0.32*
Duodenum	3.35 ± 0.27	2.29 ± 0.23*	1.20 ± 0.15*†
Liver (hepatic bed)	11.92 ± 2.87	6.02 ± 0.91	7.39 ± 1.90
Spleen	0.66 ± 0.14	0.88 ± 0.13	1.32 ± 0.17*†
Skeletal muscle	33.83 ± 8.09	32.17 ± 7.14	20.09 ± 2.38
Skin	44.50 ± 6.81	40.52 ± 7.07	37.96 ± 6.60
Brain			
Cerebral cortex	4.14 ± 0.54	1.64 ± 0.17*	1.30 ± 0.15*
Cerebellum	3.72 ± 0.29	1.89 ± 0.16*	1.27 ± 0.13*†
Pons	5.15 ± 0.47	2.51 ± 0.28*	1.59 ± 0.15*†
Medulla	5.17 ± 0.54	2.63 ± 0.27*	1.45 ± 0.14*†
Spinal cord	9.57 ± 1.14	4.86 ± 0.78*	2.83 ± 0.34*†
Myocardium			
Left ventricle	1.88 ± 0.1	0.82 ± 0.09*	0.26 ± 0.04*†
Right ventricle	3.11 ± 0.55	1.33 ± 0.13*	0.21 ± 0.01*†

Values are mean ± SE in ten dogs.

\*P &lt; 0.05 from control.

†P &lt; 0.05 from hemodilution alone.

to prevent blood flow decreases only in the medulla and spinal cord; blood flow decreased 37% in the cerebral cortex, 20% in the cerebellum, and 23% in the pons. These decreases in regional cerebral blood flow caused proportional reductions in regional cerebral oxygen supply.

Adenosine infusion increased blood flow in the left (+64%) and right (+206%) ventricular myocardium with resultant proportional increases in regional oxygen supply. Because these increases in flow oc-

Table 4. Changes in Oxygen Supply ( $\text{ml} \cdot \text{min}^{-1} \cdot 100\text{g}^{-1}$ ) in Regional Vascular Beds During Isovolemic Hemodilution Alone and During Combined Isovolemic Hemodilution and Adenosine-Induced Controlled Hypotension

	Control	Hemodilution alone	Hypotension during hemodilution
Renal cortex	105.1 $\pm$ 11.2	45.8 $\pm$ 6.2*	11.8 $\pm$ 3.4*†
Pancreas	2.8 $\pm$ 0.2	1.9 $\pm$ 0.2*	1.4 $\pm$ 0.1*†
Duodenum	7.4 $\pm$ 0.8	5.1 $\pm$ 0.6*	4.8 $\pm$ 0.7*
Liver (hepatic bed)	3.6 $\pm$ 1.3	1.8 $\pm$ 0.3*	1.0 $\pm$ 0.2*
Spleen	46.2 $\pm$ 8.1	14.5 $\pm$ 2.6*	4.9 $\pm$ 1.3*†
Skeletal muscle	0.9 $\pm$ 0.1	0.5 $\pm$ 0.1*	0.3 $\pm$ 0.1*
Skin	0.6 $\pm$ 0.1	0.3 $\pm$ 0.1*	0.2 $\pm$ 0.1*
Brain			
Cerebral cortex	6.0 $\pm$ 0.4	5.9 $\pm$ 0.3	4.4 $\pm$ 0.7*†
Cerebellum	6.3 $\pm$ 0.4	5.3 $\pm$ 0.6	4.3 $\pm$ 0.6*
Pons	4.6 $\pm$ 0.2	4.1 $\pm$ 0.5	3.4 $\pm$ 0.4*
Medulla	4.5 $\pm$ 0.3	4.1 $\pm$ 0.6	3.7 $\pm$ 0.5
Spinal cord	2.7 $\pm$ 0.3	2.1 $\pm$ 0.3	1.9 $\pm$ 0.2*
Myocardium			
Left ventricle	12.8 $\pm$ 1.1	12.8 $\pm$ 1.4	22.0 $\pm$ 3.4*†
Right ventricle	8.7 $\pm$ 1.2	7.7 $\pm$ 0.7	25.4 $\pm$ 3.5*†

Values are mean  $\pm$  SE in ten dogs.

\* $P < 0.05$  from control.

† $P < 0.05$  from hemodilution alone.

curred during aortic hypotension, they reflected disproportionate reductions in myocardial vascular resistance. When adenosine infusion was extended to 60 minutes, the effects noted above for 15 minutes of adenosine infusion persisted.

## Discussion

### *Effects of Hemodilution Alone*

The tendency for increases in cardiac output to preserve, at least partially, systemic oxygen supply during isovolemic hemodilution observed in the present study has also been demonstrated previously (15,16). In the present study, a constant heart rate implied that this increase in cardiac output was due entirely to augmented stroke volume. This finding is at variance with previous reports that increases in both heart rate and stroke volume contributed to elevated cardiac output during hemodilution (15). This apparent discrepancy is likely explained by high basal heart rates in the present study because of the vagolytic effect of pentobarbital anesthesia (17). Two major mechanisms have been proposed to account for increases in stroke volume during hemodilution: 1) increased myocardial contractility due to activation of cardiac sympathetic nerves (15) and, 2) decreased impedance to left ventricular ejection because of reduced blood viscosity and peripheral vasodilation (18).

Because blood viscosity usually remains constant, changes in calculated regional vascular resistance are often used to evaluate local adjustments in vasomotor tone. However, because reductions in blood viscosity in themselves decrease vascular resistance (19), this approach is inappropriate during hemodilution. Under these conditions, the magnitude of the reduction in viscosity must be identified so that its contribution to changes in vascular resistance can be taken into account. Although measurements of blood viscosity were not made in the present study, previous data obtained in vitro indicate that, in the range of physiologic shear rates, a 50% reduction in hematocrit causes an approximately proportional reduction in blood viscosity (16). This factor was applied to our vascular resistance data to uncover changes in regional vasomotor tone. It should be kept in mind that the quantitativeness of this approach is limited by the questionable applicability of in vitro measurements of blood viscosity to vascular beds in vivo because of regional variations in vascular dimensions and flow velocity, as well as the heterogeneity of shear rate across a single vessel (16).

In the kidney, splanchnic organs, skeletal muscle and skin, hemodilution either had no effect on flow, it reduced flow, or it caused modest increases in flow that were less than those expected from reduced blood viscosity itself. This suggests that vasoconstriction occurred in these vascular beds. Although our data shed no light on the mechanism(s) for this vasoconstriction, a role for the sympathetic vasoconstrictor nerves is suggested by several previous findings. First, cardiac sympathectomy compromises the compensatory response of the canine cardiovascular system to acute hemodilution (15). Second, arterial chemoreceptors are stimulated by diluted blood (20), which provides the obligatory sensory limb for activation of the sympathetic nerves. Finally, activation of the sympathetic vasoconstrictor nerves in peripheral beds is an important component of the reflex response to other systemic cardiovascular stresses, including hemorrhagic shock (21).

Although oxygen supply decreased in the aforementioned peripheral beds during hemodilution, this does not necessarily indicate that oxygen consumption decreased proportionally. The possibility that increases in oxygen extraction compensated at least in part for reduced oxygen carrying capacity cannot be discounted, especially in the kidney. Because of a primary function in filtering the blood, renal blood flow (and oxygen supply) is normally well in excess of that required to meet its basal oxidative demands (19). This results in a very modest local oxygen extraction, which presumably can be increased when



necessary to maintain adequate tissue oxygenation. It is worth noting that despite apparent local vasoconstriction, renal blood flow remained at baseline levels during hemodilution. This is in keeping with the well documented ability of the renal circulation for autoregulation of flow (22).

Vasoconstriction in peripheral beds ensured that much of the increase in cardiac output during hemodilution was preferentially distributed to the myocardium and brain, so that oxygen supply remained adequate to the so-called vital organs. The tendency for increases in myocardial blood flow to maintain local oxygen supply during isovolemic hemodilution has been demonstrated previously (23,24).

The present finding of >50% reduction in myocardial vascular resistance during hemodilution suggests that both lowered blood viscosity and autoregulatory coronary vasodilation contributed to these increases in myocardial blood flow. This is consistent with previous reports of reduced vasodilator reserve capacity in the coronary circulation during hemodilution (23).

The maintenance of cerebral oxygen supply during isovolemic hemodilution is in keeping with previous reports of unchanging cerebral oxygen consumption and electroencephalographic activity under comparable conditions in anesthetized dogs (25,26). The magnitude of observed changes in regional vascular resistance suggest that local vasodilation contributed to flow increases in cerebral cortex, while reduced blood viscosity alone was responsible for flow increases in subcortical regions.

In conclusion, the present results suggest that isovolemic hemodilution alone is reasonably well tolerated by body tissues, and they reaffirm its suitability for clinical use.

#### *Effects of Adenosine-Induced Controlled Hypotension during Isovolemic Hemodilution*

Adenosine-induced hypotension during isovolemic hemodilution was caused primarily by a decrease in systemic vascular resistance, although cardiac output decreased marginally because of bradycardia. This bradycardia was apparently due to direct suppression of pacemaker activity in the sinoatrial node by adenosine (27), great enough to override the expected baroreflex-mediated increase in heart rate associated with aortic hypotension itself. Such reflex tachycardia is a problem encountered frequently in patients when other drugs are employed to produce controlled hypotension.

Although local intra-arterial infusion of adenosine causes vasodilation in most organs (6,28-30) due to a

direct relaxant effect on arteriolar smooth muscle, it causes vasoconstriction in the kidney (31). This vasoconstrictor action of adenosine in the present study was demonstrated by pronounced decreases in renal blood flow, which were far in excess of those expected from reductions in driving pressure alone. The magnitude of these decreases in flow (73%) warrants concern, especially when superimposed on reduced oxygen carrying capacity of arterial blood.

Despite the direct vasodilator effect of adenosine, flow in several beds, namely the pancreas, liver, spleen, and skin, decreased during intravenous adenosine infusion. This indicates that the direct vascular effect of adenosine in these tissues was overridden by an antagonistic vasoconstrictor mechanism, perhaps the sympathetic vasoconstrictor nerves as part of the baroreceptor-reflex response to aortic hypotension (21).

Adenosine-induced controlled hypotension influenced favorably global left ventricular myocardial oxygen supply/demand balance, because it increased oxygen supply while reducing parameters of oxygen demand. The significant increase in left ventricular blood flow caused by adenosine occurred in the presence of a 50% reduction in driving pressure and after a portion of the flow reserve had been likely recruited to preserve myocardial oxygenation during hemodilution alone, which is evidence for the extensiveness of the vasodilator reserve capacity in the left coronary circulation. Another mechanism contributing to elevated left ventricular myocardial blood flow during adenosine infusion was attenuation of the systolic extravascular component of coronary vascular resistance, because of bradycardia and reduced intramyocardial pressure secondary to reduced left ventricular intracavitary pressure (32).

Reductions in heart rate and left ventricular pressure (in accordance with the law of Laplace a reflection of wall tension) were two factors reducing myocardial oxygen demand during adenosine infusion (33). Whether myocardial contractility, the third primary determinant of myocardial oxygen demand, decreased during adenosine infusion is uncertain. Although in vitro studies suggest that adenosine may inhibit transsarcolemmal movement of calcium (34), we previously observed no change in local myocardial oxygen consumption and segment shortening during intracoronary infusion of adenosine in in situ canine hearts (30,35). Although adenosine infusion significantly decreased left ventricular  $dp/dt_{max}$  in the present study, interpretation of this finding is confounded by concurrent reductions in aortic pressure and heart rate (36).

Intravascular adenosine cannot affect cerebral vas-

cular smooth muscle directly because it does not cross the blood-brain barrier (6). Therefore, changes in regional cerebral blood flow during adenosine infusion reflected responses to aortic hypotension under conditions of isovolemic hemodilution. The data indicate that autoregulatory vasodilation occurred in all regions of the brain, but that it was inadequate in higher brain regions to maintain blood flow at the level required for undiminished oxygen supply. This suggests decreases in cerebral oxygen consumption although, as stated earlier, compensatory increases in cerebral oxygen extraction cannot be ruled out. The better preservation of flow and oxygen supply in the medulla and cervical spinal cord than in higher brain regions during adenosine-induced hypotension is consistent with previous reports of heterogeneous autoregulatory capability in the brain (6,37).

The persistence of coronary and systemic hemodynamic responses during the 60-minute infusion of adenosine is confirmatory evidence that the circulation does not develop tachyphylaxis to effects of adenosine (1,35).

The present findings are directionally similar to those obtained during adenosine-induced hypotension alone (6,8). The higher blood flow in certain tissues, e.g., myocardium, is consistent with the ability of reduced blood viscosity to itself reduce vascular resistance. It should be kept in mind that this augmentation in flow occurred at the cost of reduced oxygen carrying capacity of the arterial blood.

The only other study to evaluate regional hemodynamic responses during combined isovolemic hemodilution and controlled hypotension utilized trimethaphan to induce hypotension (10). Although findings in that previous study were essentially similar to those in the present study in most vascular beds, there were glaring differences in the myocardium and kidney where combined hemodilution and trimethaphan-induced hypotension had no effect on blood flow. This contrast in results emphasizes the unique ability of adenosine to have potent but opposite vasomotor effects in the coronary and renal circulations.

In conclusion, combined isovolemic hemodilution and adenosine-induced controlled hypotension had a mixed effect on regional oxygen supply in anesthetized dogs; it increased oxygen supply in myocardium well above required levels, while it reduced oxygen supply in most other body tissues, including the brain and kidney. These latter effects suggest the need for extensive clinical monitoring of patients in whom combined isovolemic hemodilution and adenosine-induced controlled hypotension is utilized.

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# Effects of Tracheal Intubation on Laryngeal Acoustic Waveforms

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PRIEBE H-J, HENKE W, HEDLEY-WHYTE J. Effects of tracheal intubation on laryngeal acoustic waveforms. *Anesth Analg* 1988;67:219-27.

*To assess the feasibility of noninvasive detection of laryngeal injury after tracheal intubation through acoustic waveform measurements, we studied the effects of intubation on "time-expanded" acoustic waveforms of the larynx in 16 patients given general anesthesia, 9 with and 7 without tracheal intubation. Recordings of several utterances were obtained by means of a microphone and an accelerometer attached to the skin at the midpoint of the suprasternal notch. Recordings were taken the day before induction of general anesthesia, 20 minutes after extubation, and 2 and 4 days after extubation. Waveforms of the recordings were subsequently assessed visually for features different from*

*those of normal phonation as determined in preliminary studies. Waveforms in several of the recordings taken soon after extubation showed marked intraperiod and interperiod irregularities. These abnormalities improved and disappeared over the following 4 days. No changes were observed in the acoustic waveforms of seven patients given general anesthesia without tracheal intubation. The analysis of time-expanded acoustic waveforms of the larynx indicates that this technique has considerable potential as a sensitive, noninvasive technique that helps to evaluate the effects of tracheal intubation on laryngeal function, a technique that warrants further study and evaluation.*

**Key Words:** INTUBATION, TRACHEAL—complications. LARYNX, FUNCTION—postoperative.

An endotracheal tube is required during general anesthesia for controlled ventilation and airway protection. Some damage to the upper airway occurs in almost all patients after either short- or long-term intubation, and the larynx is one of the most common sites of injury, which is due primarily to pressure necrosis (1-4). The consequences of laryngeal injury, although mostly minor and reversible, are potentially serious. Laryngeal injury may lead to acute or chronic airway obstruction after extubation due to edema or granuloma formation severe enough to require surgical intervention. Laryngeal dysfunction may also lead to impaired airway protection and thus render the patient susceptible to pulmonary aspiration.

Innovations in material and shape of endotracheal tubes may help to reduce the incidence of serious sequelae in the future. Direct laryngoscopy and high-speed cinematography have been used to study laryngeal function. For practical purposes, however, a

noninvasive test would be optimal for evaluation of the effects of tracheal intubation on laryngeal performance. The purpose of this study was first to evaluate the efficacy of time-expanded acoustic waveforms of the larynx as a means of studying laryngeal function noninvasively and, second, to define changes in acoustic signals indicative of laryngeal injury after tracheal intubation.

## Methods

Preliminary studies were done in ten patients (age 21-63 years, six men, four women) to develop reliable, reproducible methods of voice recording and analysis. Six patients presented for gynecologic procedures under general anesthesia without tracheal intubation, and four of them for open heart surgery. Two of the latter patients were taking diuretics, and two of them  $\beta$ -receptor blockers. A major objective was to achieve, with minimum recording, a maximum of information. This is an important consideration because some recordings are taken when patients are still physically weak due to the preceding anesthetic and operation. To be acceptable to the patient, the test has to be quick and easy to perform.

We initially evaluated the suitability of repeating various utterances, short statements, and questions.

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These included: sustaining the vowel sound "a" for several seconds, first at a comfortable loudness and subsequently at an increased loudness; repetition of the short rapid "a" and "at"; and a pitch glide starting from as low to as high as possible.

We chose the sustained "a" for evaluation of the recorded waveforms during steady state phonation. We hypothesized that the recordings of the loud "a" might reveal subtle changes in the waveforms that would not be detected during normal loudness. The sequence of several short "a"s and "at"s was included to elicit glottal stops indicative of cord closure. The pitch glide was chosen to evaluate voice changes over a wide pitch range.

Recordings from all patients were obtained by means of a microphone held approximately 10-15 cm from the mouth and a small accelerometer (<2 g) attached to the skin with double-sided adhesive tape at the midpoint of the suprasternal notch. In such a position the transducer is typically located 2-3 cm below the glottis and its axis is oriented anteroposteriorly.

There are several advantages to the use of a pretracheal accelerometer: its signal is little influenced by supralaryngeal articulation; it produces a relatively simple waveform; and improvement in the signal-to-noise ratio can be achieved (5). The latter could be an important consideration when the speaking environment is noisy (as in a postanesthetic recovery room or an intensive care unit) and the patient's voice is weak.

The recording of the air-transmitted audio signals allowed us to differentiate between those features of the accelerometer signal attributable to laryngeal activity and those due to artifacts such as differences in accelerometer positioning or gross patient movements.

The signals recorded on magnetic tape were subsequently graphically displayed as parallel, two-channel oscillograms, typically with a time scale of 1000 mm/sec and a bandwidth of 5 kHz. To obtain these high-resolution displays, the recorded time signals were digitalized for a computer with an analog-to-digital converter. The computer subsequently displayed the signals on an electrostatic plotter.

In the preliminary studies, we tried to define features characteristic of normal phonation by visually analyzing various oscillograms. We focused our attention on changes within and between glottal periods and referred to these as intraperiod and interperiod irregularities, respectively. A period is one glottal cycle or the standard pitch period (Fig. 1, T). Reproducibility of the method was evaluated by repeating the recordings of the various utterances in

two of us (H.-J.P., W.H.) and a volunteer several times during the same session and again several days later.

After the preliminary studies we examined a further 16 patients classified into two groups. Group A consisted of nine patients who presented for open heart surgery for valvular or coronary artery disease and who were likely to have elective postoperative ventilation for 24 hours or more. There were three female and six male patients (mean age 50.6 years, range 23-65). Anesthetic drugs used included halothane, narcotics, diazepam, droperidol, pancuronium and curare. All patients were orally intubated with endotracheal tubes of appropriate sizes with low-pressure, high-volume cuffs. Mean duration of intubation was 25 hours (range 16-30).

Group B comprised seven female patients (mean age 37 years, range 14-51) given general anesthesia (mean duration 29 minutes, range 25-40) without tracheal intubation for various gynecologic procedures (dilation and curettage of the uterus, colposcopy, etc.). Anesthetic drugs used included nitrous oxide, halothane, enflurane, and thiopental. This group of patients was included to help us in differentiating between the effects of tracheal intubation and general anesthesia on acoustic waveforms of phonation.

All 16 patients were asked to repeat the following utterances, which were then recorded: (a) a long, sustained "a" at a pitch and an intensity convenient for the patient; (b) a sustained loud "a"; (c) a sequence of several short, rapid "a"s.

In group A, recordings were made in the unpremedicated patient the night before the operation, within 20 minutes after extubation, and on the second and fourth day after extubation. In group B, recordings were made in the unpremedicated patient the night before the operation, postoperatively within 20 minutes of regaining consciousness, and either later the same or the following day. No further recordings of these patients were made because they left the hospital either the same day or the day after the anesthetic.

The study was approved by the Committee on Clinical Investigation and Human Studies of Beth Israel Hospital, Boston, Massachusetts, where these studies were undertaken. Written informed consent was obtained from all patients.

## Results

### Group A

Figures 1-3 display the sequences of simultaneously recorded microphone and subglottal accelerometer

signals from the utterance "a" at a convenient level of pitch and intensity. These displays show recordings made in all nine patients in group A preoperatively (A), immediately after extubation (B), 2 days after extubation (C), and 4 days after extubation (D). Certain typical features can be extracted from several of these waveforms. The recordings of "Patient 1" (Fig. 1, A-D) may serve as an example.

The recording taken preoperatively (A) represents an amplitude-versus-time plot characteristic of normal phonation. The upper trace displays the microphone signal, the lower trace the accelerometer signal. The two channels are displayed synchronously. The microphone signal is delayed approximately 0.5 msec with respect to the accelerometer signal due to sound propagation delay. There is a sudden increase in amplitude within each period (T) of the microphone signal and a corresponding onset of a single strong stroke in the accelerometer signal (A). The oscillations decay smoothly and monotonically within each cycle. Partway through each cycle the rate of decay increases (B). These plots clearly show the periodicity of normal speech.

The preliminary studies had shown that this pattern of normal phonation is highly reproducible. The microphone recordings when repeated in the same subject immediately or days later are qualitatively and quantitatively almost identical. Only the amplitude may vary with the loudness of the voice.

The accelerometer signal is equally reproducible when recorded immediately without repositioning of the accelerometer. Although the signal is rather sensitive to even small variations in the site of application of the accelerometer, the resulting differences in the signal are primarily quantitative rather than qualitative in nature. The smooth, monotonic decay in amplitude within each period characteristic of normal phonation is highly reproducible.

The preliminary studies clearly indicated that the lack of intra- and interperiod irregularities is the most distinctive feature of normal phonation. This finding is of practical importance because the accelerometer signal may at times suggest changes in the quality of phonation due to variations in accelerometer position. However, intraperiod and/or interperiod irregularities were never observed in either two of us (H.-J.P., W.H.), in a volunteer during repeated recordings at different times, or preoperatively in any of the 16 patients studied.

In marked contrast to the smooth and regular time-amplitude plots of the preoperative recordings, the plots of the recordings taken soon after extubation (B) display marked intraperiod and interperiod irregularities. Within periods, the clear abrupt in-

crease in amplitude followed by a smooth, monotonic decay in the microphone signal, and the single strong stroke in the accelerometer signal are lost. In the accelerometer signal we notice additional deflections within the cycle (A). We have termed this phenomenon "phase reversal."

The recordings taken 2 days after extubation (C) display a clear tendency toward returning to the characteristics of normal speech that we observed in (A). The interperiod irregularities have disappeared. However, the microphone signal still shows intraperiod abnormalities. The normally smooth monotonic decay within each cycle is still interrupted by abrupt, spiky deflections. The accelerometer signal still displays "phase reversal." In general, however, these abnormal features are less pronounced than in the recording taken after extubation (B).

The plot of the recording taken 4 days after extubation (D) displays all the features of normal speech and is similar to the plot of the preoperative recording (A). All interperiod and intraperiod irregularities have disappeared.

The sequences of recordings in Patients 2-9 displayed similar characteristics. At times, however, there were only small changes in the immediately postextubation recordings (Patients 5 and 7). Both these patients were female (duration of intubation 16 and 24 hours, respectively). Whereas the microphone signals 4 days after extubation are qualitatively as well as quantitatively similar to the preoperative recordings, the accelerometer signals do not always resume their preoperative pattern. This is most likely related to a slightly different fixation of the accelerometer to the skin at the time of the final recording. In every case, however, all of the intra- and interperiod irregularities disappeared 4 days after extubation.

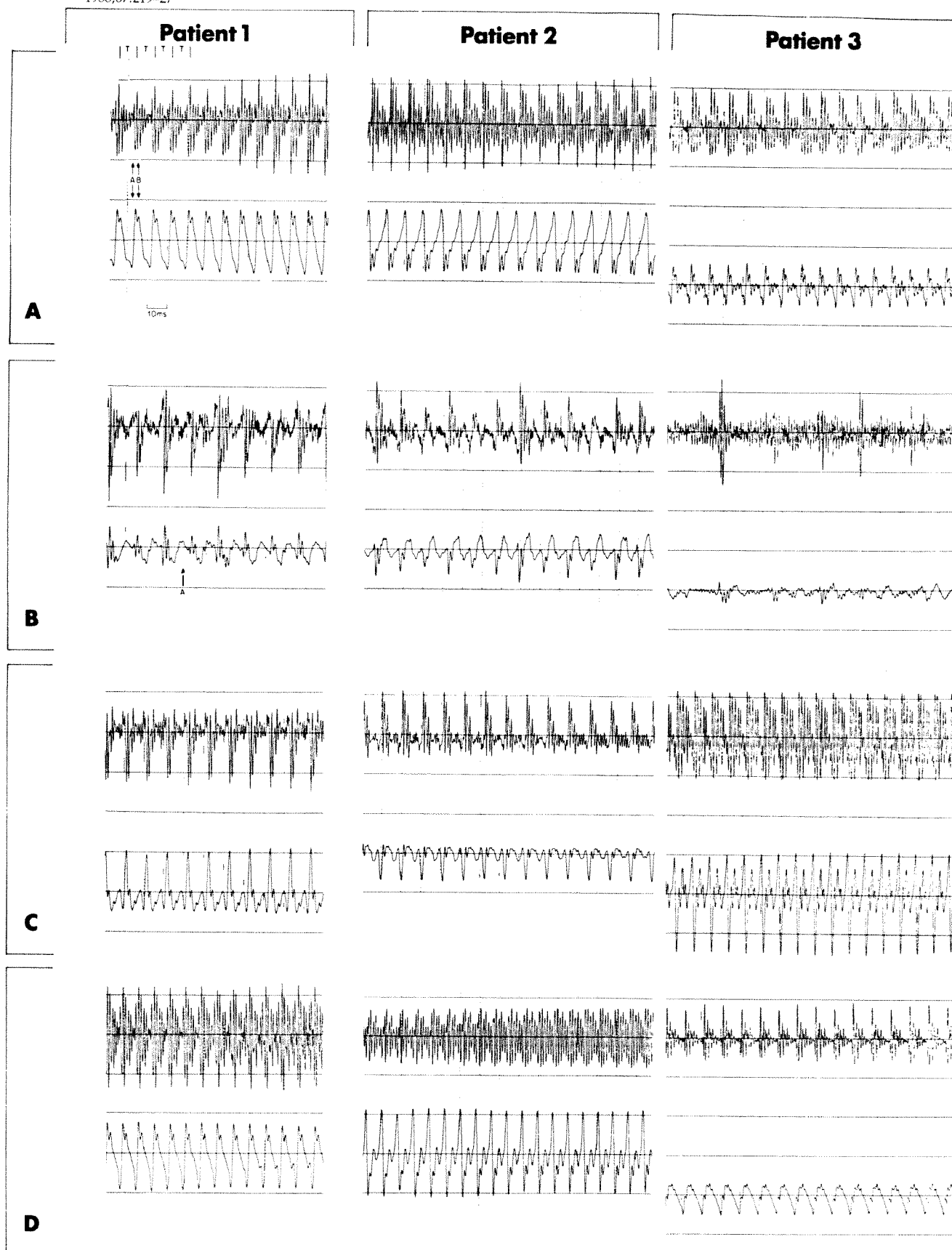
In several patients, there was poor correlation between subjectively perceived hoarseness and objectively noted changes in the acoustic waveforms. Some patients with marked hoarseness displayed fewer abnormalities in the acoustic signals than others with a lesser degree of hoarseness. There are only three displays (A-C) of Patient 5. The final recording (D) was technically inadequate.

The changes in the acoustic signals of the other utterances (loud "a," rapid "a") followed very closely those of the convenient "a." Because they did not display additional distinctive features, they are not shown.

### Group B

The recordings of this group did not show clear differences between pre- and postoperative record-





**Figure 1.** Sequences of amplitude-versus-time plots of the utterance "a" of three intubated patients. The top signal of each display represents the microphone, the bottom one represents the accelerometer signal. (A) preoperative recordings; (B) recordings immediately after extubation; (C) recordings 2 days after extubation; (D) recordings 4 days after extubation; (T) glottal cycle. For explanations of A, B, and A, see text.

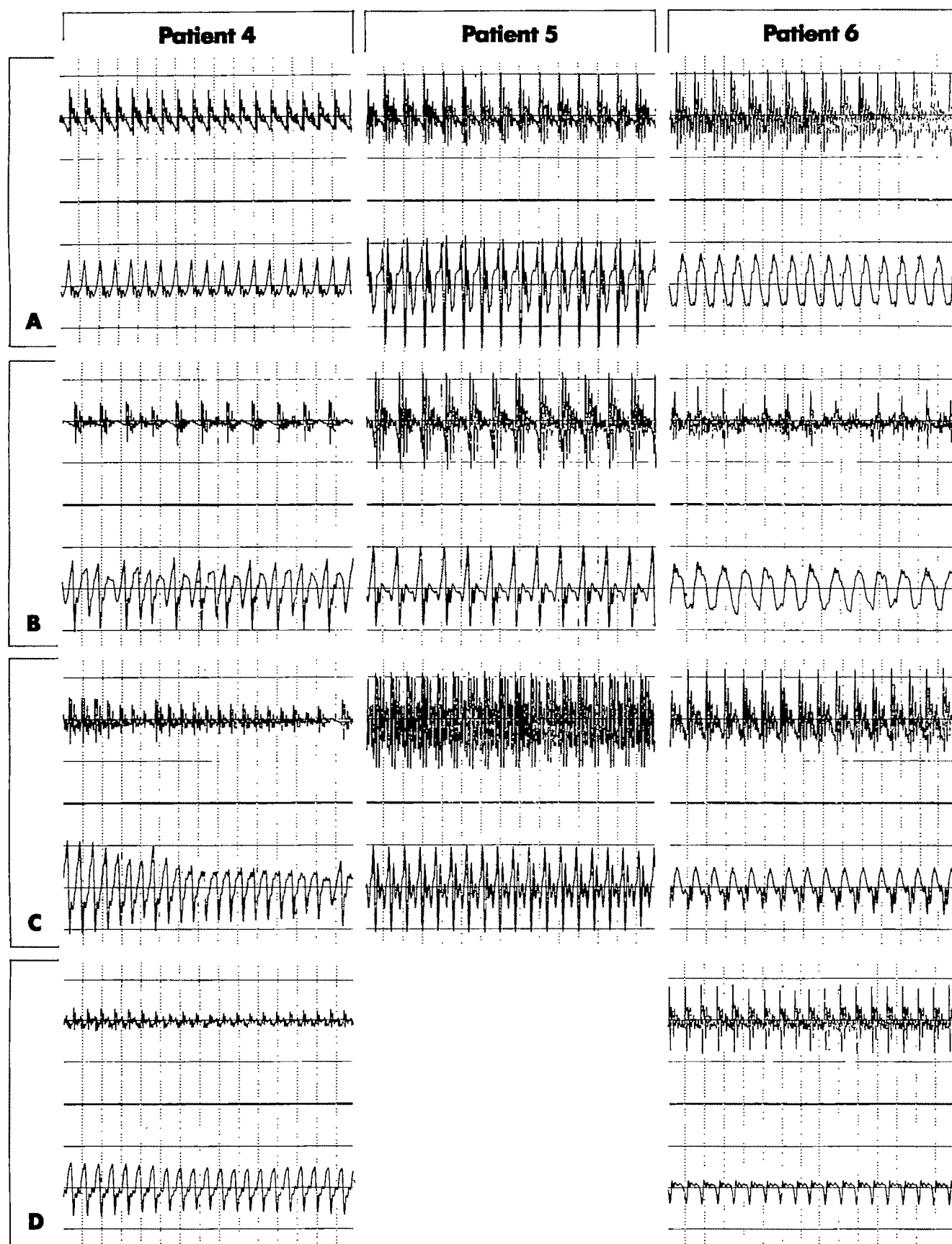


Figure 2. Sequences of amplitude-versus-time plots of the utterance "a" of three intubated patients. Abbreviations as in Fig. 1.



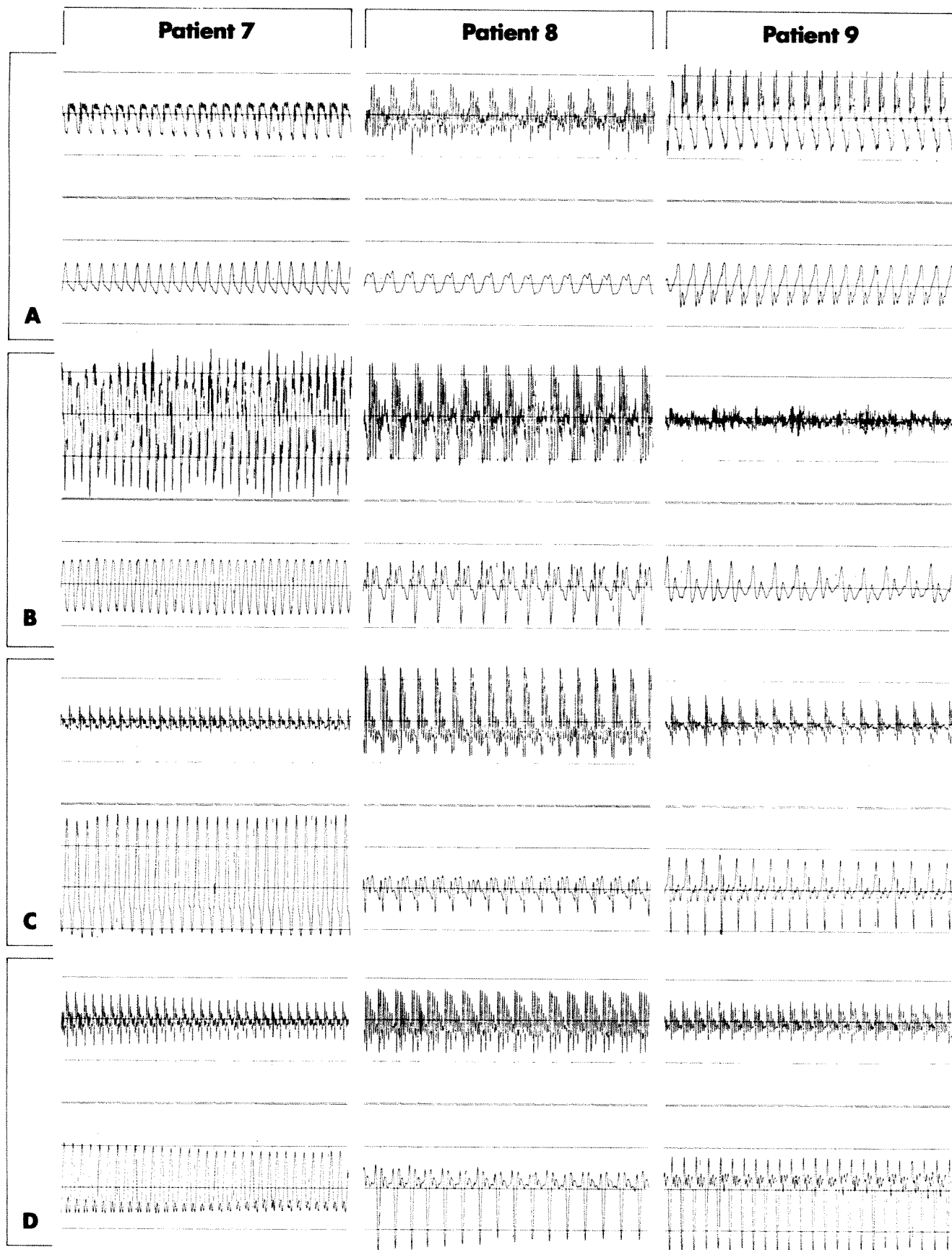
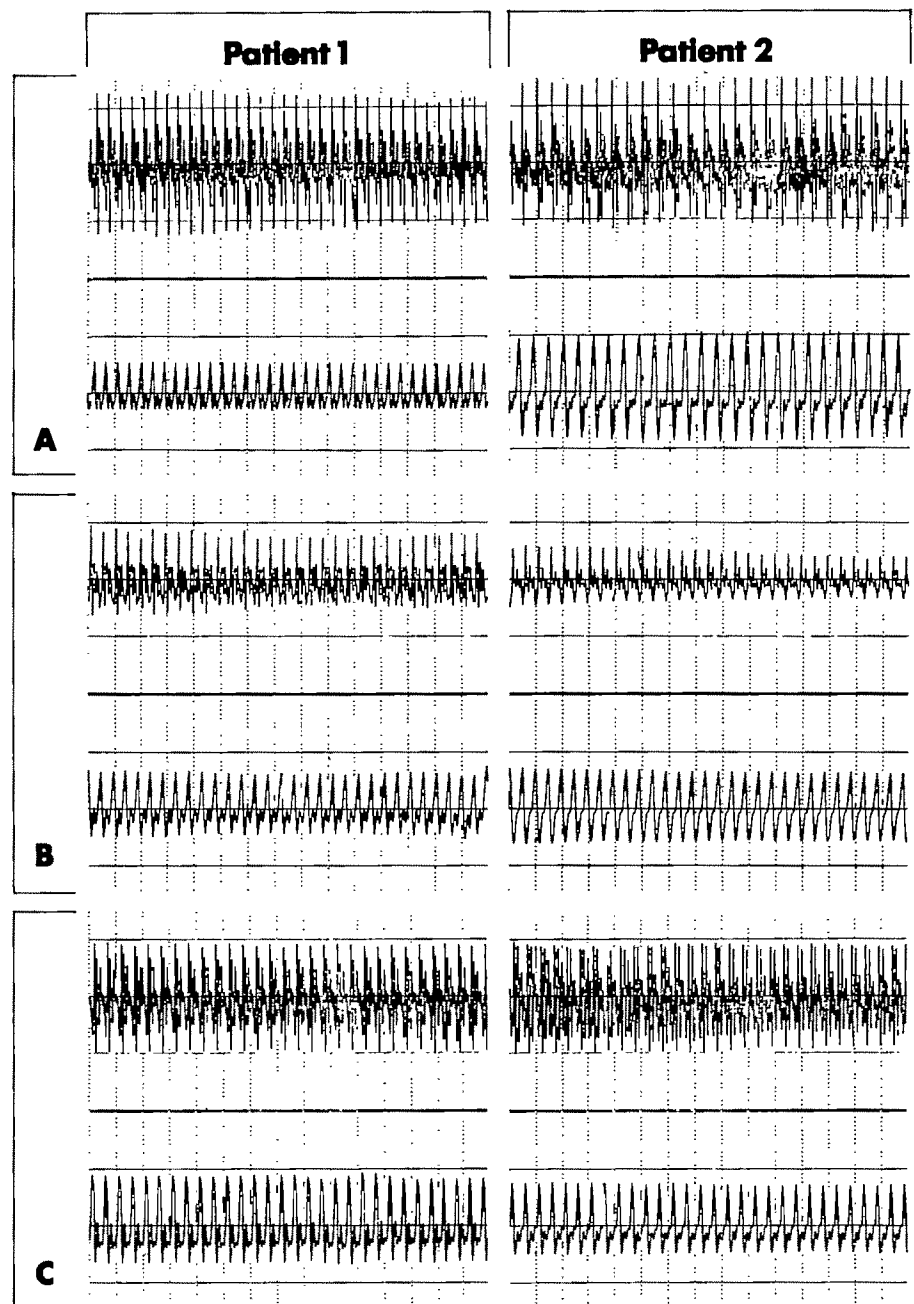


Figure 3. Sequences of amplitude-versus-time plots of the utterance "a" of three intubated patients. Abbreviations as in Figure 1.



**Figure 4.** Sequences of amplitude-versus-time plots of two nonintubated patients. (A) preoperative recordings; (B) recordings immediately after the anesthetic; (C) recordings 6-8 hours after the anesthetic.

ings. Therefore, recordings of the utterance "a" are shown for only two of the seven patients (Fig. 4).

It became obvious early on that the recordings of several of the short phrases and utterances such as the pitch glide and the short repeated "at" had to be omitted. Most patients were unable to repeat these more effort-dependent phonations immediately after extubation in a technically acceptable manner. It was also apparent from the recordings of patients who completed all phonations that no additional information could be gained from those utterances. At no

times were we able to define age- or sex-related characteristics in acoustic waveforms.

## Discussion

Laryngeal trauma, especially after prolonged tracheal intubation, remains a serious problem. Changes in tracheal tube configuration and material have diminished the incidence of injury to the larynx (6). However, the effectiveness of new tube designs needs to



be evaluated clinically, preferably by a sensitive, reproducible and, most important, by a noninvasive method. Our investigation shows that the time-expanded analysis of the acoustic waveforms of the larynx may fulfill these criteria.

The use of small accelerometers (<2 g) affixed to the external surface in the region of the larynx transduce signals reflecting various aspects of laryngeal activity during phonation. Comparative evaluation of such signals under varying conditions of articulation, transducer location, and speaker, suggests an association of specific features of the signals with mechanical and acoustical correlates such as open and closed periods during the glottal cycle and distinct subglottal and supraglottal resonances. The sudden increase in amplitude seen in the recorded microphone signals and the corresponding single strong stroke seen in the accelerometer signal within each cycle during undisturbed phonation coincide with the closure of the vocal cords. The increase in the decay rate of oscillations partway through each cycle can be attributed to the opening of the vocal cords. By displaying the motion of the vocal cords, such signals may be useful for the evaluation of airway competence. The combination of "time-expansion" (1000 mm/sec) of the acoustic waveforms and broad bandwidth provides high-resolution display that allows for visual recognition of fine features within the signals. These characteristics contribute greatly to the sensitivity of detecting laryngeal dysfunction.

The displays demonstrate that use of the pretracheal accelerometer greatly helped in waveform analysis. This is particularly evident in the recordings done immediately after extubation (Fig. 1-3, B). These were taken in a relatively noisy intensive care unit at a time when the patients' voice was often weak. When compared to the microphone signals, those originating from the accelerometer are of better signal-to-noise ratio and, therefore, better suited for waveform analysis.

During our evaluation it became apparent that analysis of the time-expanded waveforms revealed laryngeal dysfunction that could not be detected reliably by subjective, auditory means. Otolaryngologists have long used voice quality in the evaluation of laryngeal disorders. However, the assessment of voice quality in terms of breathiness, harshness, and hoarseness is prone to high intraobserver variability (7). The perception of hoarseness may even be affected by extralaryngeal factors (8). Several investigators have attempted to extract objective data from the acoustical signal that might provide criteria for the detection of laryngeal dysfunction (9-12). We concentrated our analysis on departures from periodicity in

the acoustic waveforms and on changes within each glottal cycle.

False-negative results by this method are unlikely. False-positive results, in our opinion, can be reduced to a minimum if attention is paid to details. If segments of normal and abnormal waveforms are detected within a single utterance, it is likely that the abnormal features are produced by a more temporary derangement, such as mucus on the vocal cords, rather than vocal cord edema or abrasions. The recognition of alternating patterns of waveforms is also important in excluding inadequate cooperation by the patient. In general, the voice recording requires very little effort, but it can happen that a patient is heavily sedated while the recording is being taken. Periods of normal waveforms indicate that the intermittently occurring abnormal waveforms are due to inadequate effort rather than true laryngeal dysfunction. However, time-expansion allows for adequate analysis of the waveforms of even very weak voices.

In patients given general anesthesia without tracheal intubation, we found no changes in the acoustic waveforms immediately after anesthesia. During the recording, most of the patients in this group showed more residual central depression from the preceding anesthetic than did patients who had been intubated for a prolonged period of time. This finding suggests that the observed changes in acoustic waveforms of the larynx after intubation are caused by the mechanical impact of the tracheal tube, rather than by central depression.

We did not attempt to correlate waveform irregularities with anatomic changes of the larynx. This would have required invasive examinations of the larynx, when noninvasiveness was one of the main objectives of our investigation. However, the visual assessment of many preliminary recordings enabled us to extract those features that are typical of normal phonation. We therefore feel confident in identifying those signals that are indicative of laryngeal dysfunction. Even without direct examination, our results indicate that cord function is significantly impaired directly after extubation. The follow-up recordings show that several days may be needed until the waveform pattern of normal phonation is resumed.

In summary, analysis of time-expanded acoustic waveforms may represent a sensitive, noninvasive method useful in objective detection of laryngeal impairment after tracheal intubation. It avoids some of the problems of intra- and interobserver variability inherent in simple evaluation of hoarseness. This method may, therefore, be used for the evaluation of the effects of new tracheal tubes on the larynx.

Furthermore, a voice recording taken before tracheal intubation might allow for the differentiation between preexisting laryngeal impairment and laryngeal dysfunction caused by intubation. Thus, this technique has a potential for being a sensitive, reliable method for predicting and demonstrating post-operative laryngeal complications. However, additional studies are required to reveal the potential of this technique.

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## Effects of Adenosine-Induced Hypotension on Myocardial Hemodynamics and Metabolism during Cerebral Aneurysm Surgery

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ÖWALL A, LAGERKRANSER M, SOLLEVI A. Effects of adenosine-induced hypotension on myocardial hemodynamics and metabolism during cerebral aneurysm surgery. *Anesth Analg* 1988;67:228-32.

*The effects of adenosine-induced hypotension on central as well as myocardial hemodynamics and metabolism were studied in five neurolept-anesthetized patients without known heart or lung diseases, who were undergoing cerebral aneurysm surgery. Adenosine ( $217 \pm 32 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) decreased mean arterial pressure 30% from  $77 \pm 5$  to  $54 \pm 3$  mm Hg. Cardiac filling pressures and heart rate remained unchanged during hypotension. Adenosine decreased systemic vascular resistance  $50 \pm 5\%$  while cardiac index increased  $39 \pm 10\%$ . Coronary sinus blood flow increased by  $73 \pm 13\%$  from  $128 \pm 18$  to  $224 \pm$*

*36 ml/min with a concomitant decrease in calculated coronary vascular resistance ( $66 \pm 4\%$ ). Both systemic and myocardial arteriovenous oxygen content differences decreased, and myocardial oxygen consumption decreased  $42 \pm 9\%$ . There were no alterations in myocardial fractional lactate extraction. Arterial plasma renin activity and arterial catecholamine levels were unaffected by hypotension. It is concluded that adenosine hypotension in this group of patients produced a hyperkinetic circulation in the systemic as well as in the myocardial vascular bed. Cardiac output and coronary sinus blood flow increased at the same time as myocardial oxygen consumption decreased.*

**Key Words:** ANESTHETIC TECHNIQUES, HYPOTENSIVE—adenosine. HEART—myocardial function.

Adenosine has recently been introduced as an agent to induce hypotension during intracranial aneurysm surgery (1,2). Hypotension is rapidly achieved and is caused by a marked dilation of resistance vessels, leading to a hyperkinetic circulatory pattern with an increase in cardiac output (1,2) and a minor decrease in whole body oxygen consumption (1). In contrast to other hypotensive agents such as sodium nitropruside and nitroglycerine, adenosine does not lead to activation of the renin-angiotensin system in dogs (3). This probably explains the remarkably stable blood pressure level, without tachyphylaxis or rebound hypertension, that characterizes adenosine-induced hypotension in humans (1,2).

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In animals, adenosine administered into coronary arteries is a potent vasodilator (4), and adenosine-induced hypotension by systemic administration is associated with increased coronary sinus blood flow and decreased myocardial oxygen consumption (5). In humans adenosine-induced coronary vasodilation has been demonstrated in an intraoperative study in which nonhypotensive doses of adenosine doubled coronary graft flow (6). Effects of adenosine-induced hypotension on the heart, as well as on the sympathoadrenal and renin-angiotensin systems in humans have, to our knowledge, so far not been elucidated. This investigation therefore focuses on these questions.

### Patients and Methods

Five patients (four women and one man, age 34–68 years) scheduled for intracranial aneurysm surgery were studied 2–14 days after admission for subarachnoid hemorrhage. No patient was on regular medication. Patients with cardiac or pulmonary diseases

were not included. Preoperative ECGs and chest X-rays were normal in all cases. The protocol was approved by the Human Ethical Committee of our institution and patients were included after giving their written informed consent.

One hour before operation, the patients were premedicated with diazepam 15 mg orally. Atropine 0.5 mg and droperidol 0.1 mg/kg were given intravenously before induction with thiopental 5 mg/kg and 1-2 mg phenoperidine (a synthetic opiate with longer duration but lower analgesic potency than fentanyl). Pancuronium bromide 0.1 mg/kg was given to facilitate tracheal intubation. Anesthesia was maintained with incremental doses of phenoperidine and droperidol when required. Controlled ventilation was employed with  $N_2O$  in  $O_2$  ( $FI_{O_2}$  0.4) to maintain  $Paco_2$  at approximately 4.0 kPa (30 mm Hg). Ringer's solution  $3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  was given intraoperatively. Mannitol 1 g/kg was given routinely at the start of surgery. The patients were operated on in the supine horizontal position.

After induction of anesthesia an arterial catheter was placed in the left radial artery and a flow-directed, quadruple-lumen pulmonary artery catheter (Edwards, model 93A-831-7.5F, VIP) was inserted through the left subclavian vein. A thermodilution catheter (Webster Laboratories, Altadena, California) was inserted into the coronary sinus through the right internal jugular vein under fluoroscopic control and continuous pressure recording. Its correct position in the coronary sinus was verified by analysis of blood oxygen saturation. Arterial, pulmonary arterial, right atrial, and coronary sinus pressures were continuously recorded by transducers placed at the midthoracic level. Mean pulmonary capillary wedge pressure was recorded intermittently. Cardiac output was measured by triplicate determinations using 10 ml cold saline ( $2 \pm 1^\circ\text{C}$ ) injected at end-expiration. Coronary sinus blood flow (ml/min) was determined in triplicate by the retrograde thermodilution technique, using intermittent infusions of saline at a rate of 33 ml/min. The flow values given represent the mean values of the triplicate determinations.

The ECG was monitored with a standard chest ( $V_5$ ) lead. Heart rate was determined from the R-R interval. The ECG and blood pressures were continuously recorded on a Grass polygraph. Arterial, mixed venous, and coronary sinus samples were obtained simultaneously for measurements of blood gas tensions and oxygen content. Oxygen and carbon dioxide tensions and pH were measured with an ABL 3 blood gas analyzer (Radiometer, Copenhagen). Hemoglobin oxygen saturation was obtained using an OSM 3 Hemoximeter (Radiometer) with pH and

temperature corrections. Hemoglobin concentration was also determined in each sample. Arterial and sinus blood lactate levels were measured according to Tfelt-Hansen & Sigaard-Andersen (7).

Plasma renin activity was determined in arterial blood by a radioimmunoassay method using a New England Nuclear Angiotensin  $^{125}\text{I}$  kit. Five milliliters of blood were collected from the arterial line and immediately transferred to ice-cooled glass tubes containing 5 mg ethylenediaminetetraacetic acid (EDTA). The plasma was separated from the blood cells and immediately frozen ( $-20^\circ\text{C}$ ) until analysis. Blood samples for catecholamine determination were collected through the arterial line and immediately placed in ice-cold tubes containing EDTA to a final concentration of 10 mM. After centrifugation at  $+4^\circ\text{C}$ , plasma was removed and stored at  $-70^\circ\text{C}$  until assay for concentration of epinephrine and norepinephrine (8). Arterial samples for determination of hypoxanthine and uric acid were collected and analyzed as previously described (9).

Adenosine (20 mM, 5.3 mg/L in isotonic saline prepared by the pharmacy of our institution) was administered as a continuous infusion (Critikon roller pump 2102 A) into the right atrium at a rate sufficient to reduce mean arterial pressure to approximately 55 mm Hg. Baseline measurements and blood samplings were made before the infusion of adenosine and after 20 minutes of stable hypotension. Final measurements and blood samples were obtained 20 minutes after the termination of adenosine infusion.

### Calculations and Statistics

Systemic and pulmonary vascular resistance indexes as well as left and right ventricular stroke work indexes were calculated according to standard formulas. Coronary vascular resistance was calculated as (diastolic arterial pressure - pulmonary capillary wedge pressure)/coronary sinus flow. Myocardial fractional lactate extraction was calculated as (arterial lactate concentration - sinus lactate concentration)/arterial lactate concentration, and converted to percent. Data were analyzed using two-way analysis of variance with randomized block design with multiple comparisons.  $P < 0.05$  was accepted as significant. Results are expressed as mean  $\pm$  SEM.

### Results

Controlled hypotension, induced during dissection and clipping of the aneurysms and lasting for 25-37 minutes, usually commenced 3-4 hours after initiation of anesthesia. Adenosine ( $217 \pm 32 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) reduced mean arterial and diastolic



Table 1. Systemic and Myocardial Hemodynamic Variables Before, During, and After Adenosine-Induced Hypotension in Five Patients During Neurosurgery

	Before adenosine	Adenosine	After adenosine
Mean arterial pressure (mm Hg)	77 ± 5	54 ± 3†	79 ± 3
Diastolic arterial pressure (mm Hg)	61 ± 5	40 ± 4†	61 ± 4
Mean pulmonary artery pressure (mm Hg)	14 ± 2	16 ± 2	14 ± 1
Mean pulmonary capillary wedge pressure (mm Hg)	8 ± 2	10 ± 2	9 ± 1
Mean right atrial pressure (mm Hg)	5 ± 1	6 ± 1	6 ± 1
Mean coronary sinus pressure (mm Hg)	8 ± 1	8 ± 1	8 ± 1
Cardiac index (L·min <sup>-1</sup> ·m <sup>-2</sup> )	2.2 ± 0.2	3.1 ± 0.4*	2.7 ± 0.2
Coronary sinus blood flow (ml/min)	128 ± 18	224 ± 36†	162 ± 27
Heart rate (beats/min)	63 ± 6	67 ± 7	65 ± 7
Stroke volume index (ml·m <sup>-2</sup> )	36 ± 5	46 ± 4	44 ± 5
Left ventricular stroke work index (mm Hg·ml·m <sup>-2</sup> )	2567 ± 414	2012 ± 226	2990 ± 371
Right ventricular stroke work index (mm Hg·ml·m <sup>-2</sup> )	319 ± 69	446 ± 58*	361 ± 67
Systemic vascular resistance index (mm Hg·L <sup>-1</sup> ·min·m <sup>2</sup> )	34 ± 3	17 ± 3†	28 ± 2
Pulmonary vascular resistance index (mm Hg·L <sup>-1</sup> ·min·m <sup>2</sup> )	2.9 ± 0.4	2.1 ± 0.4	1.9 ± 0.4
Coronary vascular resistance (mm Hg·L <sup>-1</sup> ·min)	453 ± 71	151 ± 26†	386 ± 81

Values are mean ± SEM.

\*P &lt; 0.05, significantly different from before and after adenosine.

†P &lt; 0.01, significantly different from before and after adenosine.

arterial pressures  $30 \pm 3$  and  $34 \pm 3\%$ , respectively (Table 1). There was no need for dose adjustments during the hypotension period. Mean pulmonary artery, mean pulmonary capillary wedge, mean right atrial, and mean coronary sinus pressures were unaffected. Cardiac index increased  $39 \pm 10\%$  while heart rate remained unchanged. Left ventricular stroke work index was unaffected but right ventricular stroke work index increased ( $53 \pm 20\%$ ). Adenosine decreased systemic vascular resistance ( $50 \pm 5\%$ ), while pulmonary vascular resistance was unaffected. Coronary sinus blood flow increased  $73 \pm 13\%$  (Table 1, Fig. 1).

Arterial  $P_{O_2}$  was  $15.9 \pm 1.9$  kPa ( $119 \pm 14$  mm Hg) and  $P_{CO_2}$  was  $3.9 \pm 0.1$  kPa ( $29 \pm 1$  mm Hg) before adenosine administration and there were no significant alterations during the infusion (Table 2). Arterio-pulmonary artery oxygen content difference decreased  $34 \pm 4\%$  while whole body oxygen consumption was unaltered. Coronary sinus oxygen content increased  $103 \pm 19\%$  and arterio-coronary sinus oxygen content difference thereby decreased  $66 \pm 4\%$ . Myocardial oxygen consumption decreased  $42 \pm 9\%$ . Blood concentrations of lactate and fractional myocardial lactate extraction were unaltered by adenosine (Table 2). The  $V_5$  lead of the ECG showed no ST-T segment changes. One patient had an intermittent secondary AV-block during induction of hypo-

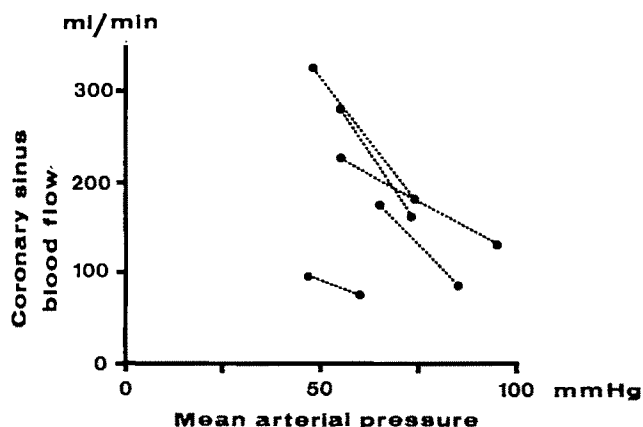


Figure 1. Illustration of coronary sinus blood flow and mean arterial pressure, before and during adenosine-induced hypotension in five patients during neurosurgery.

tension. This arrhythmia was, however, abolished once the hypotension reached steady state.

Renin activity in arterial plasma ( $3.6 \pm 1.4$   $\mu\text{g/L}$ ) was unaffected by adenosine hypotension, and plasma catecholamines did not change significantly (Table 3). The levels of the adenosine metabolites hypoxanthine and uric acid increased in arterial plasma during the adenosine infusion but had returned toward baseline values 20 minutes after the termination of the infusion (Table 3). The postoperative course was uneventful in all cases.

Table 2. Systemic and Myocardial Metabolic Variables Before, During, and After Adenosine-Induced Hypotension in Five Patients During Neurosurgery

	Before adenosine	Adenosine	After adenosine
Arterial Po <sub>2</sub> (kPa)	15.9 ± 1.9	15.3 ± 1.8	14.9 ± 1.3
(mmHg)	119 ± 14	115 ± 13	112 ± 10
Arterial Pco <sub>2</sub> (kPa)	3.9 ± 0.1	3.9 ± 0.04	4.2 ± 0.1
(mmHg)	29 ± 0.5	29 ± 0.3	32 ± 0.8
Coronary sinus oxygen content (ml/L)	65 ± 5	126 ± 4†	73 ± 5
Arteriopulmonary artery oxygen content difference (ml/L)	41 ± 3	27 ± 2*	37 ± 4
Arteriacoronary sinus oxygen content difference (ml/L)	102 ± 5	35 ± 5†	89 ± 8
Whole body oxygen consumption (ml/min)	151 ± 17	135 ± 13	166 ± 13
Myocardial oxygen consumption (ml/min)	13 ± 2	8 ± 2*	15 ± 3
Arterial lactate concentration (mmol/L)	1.3 ± 0.2	1.6 ± 0.3	1.5 ± 0.3
Coronary sinus lactate concentration (mmol/L)	0.9 ± 0.2	1.2 ± 0.3	1.3 ± 0.2
Myocardial fractional lactate extraction (%)	30 ± 5	30 ± 4	21 ± 6

Values are mean ± SEM.

\*P < 0.05, significantly different from before and after adenosine.

†P < 0.01, significantly different from before and after adenosine.

## Discussion

Adenosine infusion ( $217 \pm 32 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) reduced mean arterial pressure  $30 \pm 3\%$ . This reduction in blood pressure was attributed to reduced systemic vascular resistance secondary to arterial vasodilation. There were no signs of venodilation judging from the unaffected cardiac filling pressures. The maintained myocardial filling pressures may also have been mediated by a redistribution of blood flow from splanchnic to other vascular beds, as has been demonstrated in dogs during ATP-induced hypotension (10). The preferential afterload reduction was associated with increased cardiac output while whole body arteriovenous oxygen content difference decreased. Such hyperkinetic circulatory pattern, with minor influence on heart rate during adenosine hypotension, was also found in previous studies in humans (1,2).

Despite the reduced myocardial perfusion pressure, adenosine increased coronary sinus blood flow with a resultant doubling of coronary sinus oxygen content. This indicates the presence of coronary vasodilation. Although the decrease in left ventricular stroke work index did not reach statistically significant levels in this limited number of patients, decreased left ventricular work has been indicated in

Table 3. Plasma Renin Activity, Uric Acid, Hypoxanthine and Catecholamine Concentrations in Arterial Plasma Before, During, and After Adenosine-Induced Hypotension in Five Patients During Neurosurgery

	Before adenosine	Adenosine	After adenosine
Plasma renin activity ( $\mu\text{g/L}$ )	4.1 ± 1.6	3.5 ± 1.3	4.7 ± 1.5
Uric acid ( $\mu\text{mol/L}$ )	196 ± 48	282 ± 71*	269 ± 51
Hypoxanthine ( $\mu\text{mol/L}$ )	1.6 ± 0.8	8.8 ± 0.6†	2.5 ± 0.8
Epinephrine (nmol/L)	0.15 ± 0.03	0.10 ± 0.02	0.11 ± 0.02
Norepinephrine (nmol/L)	0.12 ± 0.02	0.20 ± 0.07	0.15 ± 0.02

Values are mean ± SEM.

\*P < 0.05, significantly different from before and after adenosine.

†P < 0.01, significantly different from before and after adenosine.

larger studies (1,2). On the other hand, right ventricular work increased as a result of increased cardiac index and maintained pulmonary arterial and right atrial pressures. Right ventricular myocardial work was 10–20% of left ventricular work. However, because the sum of left and right ventricular work did not increase during adenosine hypotension, the increased coronary sinus flow was not related to increased myocardial work. The magnitude of coronary vasodilation was comparable to that found in canine studies of adenosine-induced hypotension (5,11) but smaller than that during ATP-induced hypotension (12,13).

It has previously been demonstrated that adenosine produces marked vasodilation in human vascular beds in the brain (14) and skeletal muscle (9,15). The adenosine-induced increase in cerebral blood flow during neuroleptic anesthesia is influenced by the ventilatory pattern to the extent that the increase in flow is attenuated by moderate hyperventilation (14). The present study demonstrates that a corresponding level of hyperventilation (Paco<sub>2</sub> 30 mm Hg) did not affect the adenosine-induced increase in coronary blood flow.

The hypotension was associated with a 40% decrease in myocardial oxygen consumption. This marked decrease in oxygen utilization is in agreement with canine studies of adenosine-induced hypotension (5) and may reflect decreased myocardial work and/or reduced oxygen utilization not related to changes in myocardial work. An oxygen sparing effect of adenosine unrelated to myocardial work has been reported in dogs (16). A calcium channel blocking effect of adenosine may also exist, at least in vascular smooth muscle (17). The marked reduction



in myocardial oxygen uptake was not associated with change in myocardial lactate turnover.

Controlled hypotension induced by vasodilators such as sodium nitroprusside may be associated with tachyphylaxis during hypotension and rebound hypertension after discontinuation of the infusion (18,19). These side effects are considered to be caused by activation of the renin-angiotensin system mediated by reduced renal perfusion pressure and increased sympathoadrenal activity (20,21). Unaltered plasma renin activity has been reported in dogs during adenosine-induced hypotension, while sodium nitroprusside and nitroglycerine enhanced renin release (3). The effect of adenosine on renin mechanisms is probably mediated by a direct inhibition of the renal juxtaglomerular cells (22,23). The present study demonstrates unchanged renin activity and unchanged levels of circulating catecholamines in arterial plasma during adenosine-induced hypotension. Absence of sympathetic activation and adenosine-induced inhibition of renin activation may explain the stable hypotensive effect without dose adjustments in our patients, as well as in previous studies with adenosine (1,2).

In conclusion, adenosine-induced hypotension in neurolept-anesthetized patients was associated with a significant increase in coronary blood flow together with decreased myocardial oxygen consumption. The stability of the adenosine-induced hypotension is probably due to inhibition of both the sympathoadrenal and the renin-angiotensin system.

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## Comparison of Buprenorphine with Morphine in the Treatment of Postoperative Pain in Children

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Comparison of buprenorphine with morphine in the treatment of postoperative pain in children. *Anesth Analg* 1988;67:233-9.

*The safety and efficacy of buprenorphine and morphine as postoperative analgesics for children were compared in 60 boys and girls 4 to 14 years old having elective orthopedic operations on upper or lower extremities. The drugs were given in a double-blind manner initially intravenously and thereafter by sublingual buprenorphine or intramuscular morphine administered as required to relieve pain until the third postoperative morning. The IV dose needed to achieve*

*complete initial analgesia was  $5.2 \pm 2.8$   $\mu\text{g/kg}$  buprenorphine and  $166 \pm 100$   $\mu\text{g/kg}$  morphine. The duration of effect was significantly longer with buprenorphine than with morphine,  $248 \pm 314$  and  $114 \pm 109$  minutes, respectively ( $P = 0.03$ ). The most common side effects were nausea and vomiting (28 and 16%) and urinary retention (21 and 19%) in the buprenorphine and morphine groups, respectively. Analgesia with sublingual buprenorphine was as effective and reliable as with intramuscular morphine but a longer duration of action could not be demonstrated.*

Key Words: ANALGESICS—buprenorphine, morphine. PAIN, POSTOPERATIVE—pediatric. ANESTHESIA—pediatric.

Pediatric patients are given less postoperative analgesics compared with adults (1) and the analgesic therapy has been reported by children to be inadequate (2). To some extent the inadequacy of postoperative analgesia in children may be related to their unwillingness to accept frequent injections of analgesics. The relatively long analgesic effect of buprenorphine might help to overcome this problem. Additionally the sublingual preparation of buprenorphine might make injections unnecessary. Intravenous buprenorphine has been shown to be a safe postoperative analgesic when given to young children (3). Sublingual buprenorphine has proved to be a useful postoperative analgesic in adults (4,5). To our knowledge the safety and efficacy of sublingual buprenorphine as postoperative analgesic has not been evaluated in pediatric patients.

The purpose of this study was to compare buprenorphine with morphine as postoperative analgesics when given to children following orthopedic surgery.

The analgesics were initially given intravenously in the recovery room and, thereafter, on the ward sublingually (buprenorphine) and intramuscularly (morphine) until the third postoperative morning.

### Patients and Methods

The study protocol was approved by the ethical committee of our institution. Sixty male or female children undergoing elective upper or lower limb orthopedic surgery (e.g., osteotomy, de-rotation, hip correction, Keller's operation, or tendo-Achilles extension), aged between 4 and 14 years and weighing between 13 and 60 kg whose parents had given informed consent, were included in the study.

Children with muscular dystrophies, myopathy, cerebral palsy, severe hepatic or renal dysfunction, marked ventilatory impairment due to underlying respiratory disease, or increased intracranial pressure were excluded from the study, as were those unable to take a sublingual tablet. In addition, patients considered to be poor anesthetic risks (i.e., not ASA class 1 or 2) and those known to be sensitive to buprenorphine or morphine were excluded from the study.

A randomized, double-blind, multiple-dose study design was used. Following orthopedic surgery, the patients received multiple doses as required of either

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buprenorphine (3  $\mu\text{g/kg}$ ) or morphine (100  $\mu\text{g/kg}$ ) intravenously, while in the recovery room. After transfer to the ward, the patients received either sublingual buprenorphine (approximately 6  $\mu\text{g/kg}$ ) with an intramuscular placebo injection or intramuscular morphine (150  $\mu\text{g/kg}$ ) with placebo sublingual tablet(s) as clinically indicated. Patients were studied up to the third postoperative morning.

The active buprenorphine solution and sublingual tablets were provided by Reckitt & Colman, Pharmaceutical Division (Kingston-upon-Hull, England) together with placebo tablets manufactured to look identical to the active tablets. Morphine hydrochloride (Morphin, Medica, Finland) was used as the IV/IM morphine preparation. The randomization and blinding was performed by the Pharmacy of the Helsinki University Central Hospital, where the study drugs were packed.

### *Premedication and Anesthesia*

A standard premedication and anesthetic technique was used for all patients. This involved premedication with flunitrazepam (0.1 mg/kg up to a maximum of 2.0 mg total) approximately 1.5 hours before surgery and administration of intravenous glycopyrrolate immediately before induction of anesthesia. Induction was achieved with thiopental (2–4 mg/kg) with muscle relaxation using pancuronium as indicated. Patients were intubated and ventilated to normocarbica with  $\text{N}_2\text{O}/\text{O}_2$  7:3 with supplemental enflurane given according to clinical signs. Reversal of muscle relaxation was achieved with standard doses of glycopyrrolate and neostigmine. The times of incision and completion of operations were recorded.

### *Analgesic Therapy*

Personal analgesic packs containing ampules for intravenous administration in the recovery room and ampules and sublingual tablets for use on the ward were issued to each patient by the hospital pharmacy. Ampules (3 ml) for use in the recovery room were identical in appearance and contained either buprenorphine (0.3 mg/ml) or morphine (10 mg/ml). Ampules (3 ml) for use on the surgical ward were identical in appearance and contained either morphine (10 mg/ml) or physiological saline. All sublingual tablets were identical in appearance and contained either 0.1 mg, 0.15 mg, or 0.2 mg buprenorphine, or were placebo. In order to maintain double-blind conditions, the placebo injections and placebo sublingual tablets, packed as single doses,

were included in the ward packs. Analgesic packs were allocated randomly so that half of the patients received buprenorphine and half received the morphine treatment.

In the recovery room each patient received, according to clinical requirements, 0.01 ml/kg of their allocated analgesic intravenously (i.e., 3  $\mu\text{g/kg}$  buprenorphine or 100  $\mu\text{g/kg}$  morphine). This was repeated every 5 to 15 minutes until the patient was free of pain and later repeated again if necessary. The pain was assessed by an observer (a member of the research group or a research nurse) from 0 (no pain) to 9 (worst possible pain). The patient used a verbal 4-point scale (0, no pain; 3, severe pain) and two different visual analog scales (6). Sedation was assessed on a 5-point scale from 0 (awake) to 4 (asleep). Additionally, a record was made of vital signs and any side effects. Assessments were made 5 and 15 minutes after injection and every 15 minutes thereafter until an additional dose of analgesic was considered necessary by the observer. The same sequence of assessments were made after all further administrations while in recovery room. The patient was returned to the ward after at least 2 hours, when calm and free of pain.

On the surgical ward, analgesics were administered from the patient's treatment pack according to clinical requirements and the time of each dose was recorded. Not more than six doses were administered during 24 hours. Each administration consisted of an intramuscular injection of either morphine (150  $\mu\text{g/kg}$ ) or placebo and one or two sublingual tablets of either buprenorphine (approximately 6  $\mu\text{g/kg}$ ) or placebo. Doses of sublingual tablets were given on a body weight basis according to the following schedule: Weight range (kg): sublingual tablets

13–20	0.10 mg buprenorphine or 1 $\times$ placebo
21–29	0.15 mg buprenorphine or 1 $\times$ placebo
30–37	0.20 mg buprenorphine or 1 $\times$ placebo
38–45	0.25 mg buprenorphine or 2 $\times$ placebo
46–53	0.30 mg buprenorphine or 2 $\times$ placebo
54–62	0.35 mg buprenorphine or 2 $\times$ placebo

The nurses recorded their impression of the test analgesic three times in 24 hours at the end of each shift and the investigator recorded the patient's impression of the analgesic once daily in the morning. These assessments were on a 5-point scale of very good (1), good (2), fair (3), poor (4), or very poor (5). Side effects were also recorded. If the test medication did not provide sufficient analgesia, the patient was withdrawn from the study and treated as necessary. A record of all other medications used during the immediate pre- and poststudy periods (including

**Table 1.** Demographic Data and Duration of Operation by Treatment Group

	Buprenorphine (n = 28)	Morphine (n = 32)	P Value
Boys/girls	11/17	22/10	<0.05
Age (yr)	10.4 ± 3.2	9.9 ± 2.9	NS
Weight (kg)	33.7 ± 12.2	33.8 ± 11.8	NS
Height (cm)	137 ± 22	136 ± 21	NS
Duration of operation (min)	109 ± 67	110 ± 74	NS

Results are number of patients and mean ± sd.

alternative analgesia if the patient was withdrawn) was made. Assessments on the surgical ward were performed from the operation day (Day 1) to the morning of the third postoperative day (Day 3).

### Statistical Analysis

Statistical analysis was performed by using a Mann-Whitney *U* test and a  $\chi^2$  test as appropriate. The mean doses for complete initial analgesia, analgesic consumption and the times of onset of analgesia together with the duration of analgesia were compared with the Student's *t*-test for unpaired data. Two-way analysis of variance was used to compare body temperatures between the study groups and changes from the first measured value.

### Results

A total of 60 patients were recruited into the study; 28 were given buprenorphine, 32 received morphine. Although randomization did not result in 30 patients in each treatment group, the numbers were sufficient for statistical comparisons to be made between the two groups. Three patients entered the study on two separate occasions. Both entries of these patients have been included in the analysis because the interval between the entries was long and each patient received different treatments on the two occasions.

### Demography and Surgery

The demographic data for the patients are summarized by treatment group in Table 1. Significantly more males were in the morphine group than in the buprenorphine group ( $P < 0.05$ ). Analysis of the data for age, weight, and height showed no significant differences between patients in the treatment groups.

Operations, mainly on the upper or lower limbs, were similar in the two treatment groups. There was no statistically significant difference between the two groups with respect to duration of surgery (Table 1).

### Recovery Room

The dose of each analgesic that was needed to produce complete initial analgesia according to the observer, the time of onset of action as evaluated by the observer and the child, and the duration of effect are shown in Table 2. During the titration to complete initial analgesia 16/28 of the buprenorphine patients and 17/32 of the morphine patients fell asleep. The mean time of onset of complete initial analgesia as judged by patients who did not fall asleep was also calculated. The duration of effect of the initial dose was significantly longer with buprenorphine than with morphine ( $P = 0.029$ ). The potency ratio of buprenorphine to morphine for complete initial analgesia was 31.5:1.

The assessment of sedation showed most patients to be between "moderately drowsy" and "asleep" while in the recovery room. Buprenorphine produced significantly more sedation ( $P < 0.05$ ) than did morphine during the first hour after each of the first 3 IV doses.

Systolic and diastolic blood pressures, heart rate, and ventilatory rate before the analgesic and on leaving the recovery room were compared. There were no changes in heart rates. The small but statistically significant decreases in the blood pressures (in buprenorphine group from 120/65 to 114/58 mm Hg, in morphine group from 121/68 to 114/61 mm Hg) did not differ between the treatments. Patients given buprenorphine had a greater decrease in ventilatory rate than did those given morphine, 32 and 10%, respectively ( $P = 0.0008$ ). The changes were not of sufficient magnitude to cause clinical concern. Following 6  $\mu\text{g/kg}$  of buprenorphine the ventilatory rate of one patient decreased gradually from 22 to 8 breaths/min during 1 hour 45 minutes. Clinically the ventilation was judged to be adequate and the only action taken was to encourage the patient to breathe.

There were only a few unwanted side effects in the recovery room. Two patients in the buprenorphine group and one in the morphine group had nausea and vomiting. Two children in the buprenorphine group were unduly drowsy and two in the morphine group had a rash, one of them locally along the vein.

### Surgical Ward

The individual doses of sublingual buprenorphine varied from 5.0 to 7.1  $\mu\text{g/kg}$ . The IM morphine dose was always 150  $\mu\text{g/kg}$ . The mean ( $\pm$  sd) total doses of the analgesics given on the ward on each day are shown in Table 3. The mean number of doses given each day on the ward was not statistically significantly different in the two groups. Patients given



Table 2. Characteristics of Buprenorphine and Morphine Given Intravenously by Titration in the Recovery Room

	Buprenorphine (n = 28)	Morphine (n = 32)	P Value
Dose for complete initial analgesia ( $\mu\text{g/kg}$ )	5.2 $\pm$ 2.8	165 $\pm$ 100	—
Time of onset of complete initial analgesia			
By the observer (min)	11.8 $\pm$ 7.6 (5–35)*	16.1 $\pm$ 12.2 (5–50)*	0.102
By the patient† (min)	12.1 $\pm$ 5.4 (5–20)*	31.7 $\pm$ 34.3 (5–110)*	0.047
Duration of effect (min)	248.4 $\pm$ 314.4	113.8 $\pm$ 109.2	0.029

Results are mean  $\pm$  SD.

\*Range.

†Number of patients awake in the buprenorphine (n = 12) and morphine (n = 15) groups.

Table 3. Analgesic Consumption by Treatment Group and Buprenorphine–Morphine Potency Ratios

	Buprenorphine ( $\mu\text{g/kg}$ ) (n = 28)	Morphine ( $\mu\text{g/kg}$ ) (n = 32)	Potency ratio (Buprenorphine/morphine)
First day			
In the recovery room during 2 hours (IV)	7.6 $\pm$ 4.0	288 $\pm$ 126	37.8 : 1
On the ward (SL/IM)	14.1 $\pm$ 7.2	347 $\pm$ 150	24.5 : 1
Total	21.8 $\pm$ 9.0	634 $\pm$ 199	
Second day (SL/IM)	20.7 $\pm$ 8.3	515 $\pm$ 219	24.9 : 1
Third day (SL/IM)	13.9 $\pm$ 9.9 (n = 23)	352 $\pm$ 209 (n = 29)	25.2 : 1

Results are mean  $\pm$  SD.

SL, sublingual.

buprenorphine received a mean of 2.3, 3.6, and 2.5 doses and the morphine patients a mean of 2.3, 3.4, and 2.4 doses, on days 1, 2 and 3, respectively. During the 3 days, ten children receiving buprenorphine reported on 17 occasions that their analgesia was poor or only satisfactory. In nine of these children, average to high total buprenorphine doses, compared with the mean doses, had been given (17.2–37.5  $\mu\text{g/kg}$ ); in one child the dose was low (10.0  $\mu\text{g/kg}$ ). Eleven of the 32 children given morphine considered the analgesic therapy to be only satisfactory or poor on 17 occasions. In seven of these cases the daily morphine dose given (150–450  $\mu\text{g/kg}$ ) was lower than the mean daily dose.

The majority of patients in both treatment groups completed the study. The most common reason for early withdrawal was insufficient analgesic effect (three buprenorphine patients; one morphine patient). One patient in both study groups had to be withdrawn because of their reluctance to accept injections.

The three daily nurses' assessments of the postoperative analgesia generally compared favourably with those of the patients' assessments. However, there were three children in the buprenorphine and five in the morphine group who did not consider their analgesic therapy good, although the nurse did. On the other hand, in four cases in the buprenorphine

group and five in the morphine group in which unwanted effects were reported, the nurse considered the analgesic therapy only satisfactory or poor although the child rated it good.

Unwanted side effects reported during the study on the surgical ward are summarized in Table 4. the most common were nausea and/or vomiting and urinary retention. There were no statistically significant differences in the incidence of side effects between the groups. No patient needed to be withdrawn from the study because of side effects.

A number of patients were given antipyretic analgesics (aspirin, two; paracetamol, nine; indomethacin, one) during the study for the treatment of fever  $>38.5^\circ$  in ten cases and headache in two cases. Significantly more patients in the morphine group (11) than in the buprenorphine group (1) received these drugs ( $P < 0.05$ ). Pain relief scores of these 11 children in the morphine group were equal to the scores of the whole morphine group as well as their morphine consumption, 600, 518, and 375  $\mu\text{g/kg}$  on the first, second, and third day, respectively. Recording of the body temperature was not part of the study protocol but is a routine in surgical postoperative patients. The morning and evening temperatures were analyzed together with frequency of use of antipyretics, if any. The mean body temperature in the morphine group was higher than that in the

Table 4. Unwanted Side Effects

	Buprenorphine (n = 28)	Morphine (n = 32)
Vomiting/nausea	8	5
Micturition difficulties/urinary retention	6	6
Drowsiness	2	0
Confusion	1	1
Dizziness	2	0
Headache	1	2
Bad dreams	0	1
No side effects	13	19

buprenorphine group throughout the study period (Table 5). According to the two-way analysis of variance, the temperature increase from the first value was highly significant as well as the difference between the study groups.

## Discussion

In recent years the undertreatment of children's pain, including postoperative pain, has been reported from several centers (1,2), and it has been pointed out that education of nurses and pediatric surgeons on this topic is neglected (7). However, discovery of the problem does not necessarily result in an improvement of the situation. Children do not approve of the same kind of analgesic therapy as do adults. On the other hand we have very few pharmaceutical preparations to offer to children. Tablets and suppositories, designed for use in adults, make it difficult to give accurate doses in small children. Very little has been reported on the efficacy and safety of narcotic and antipyretic analgesics when used postoperatively for children.

One of the major difficulties is the reluctance of children to accept injections. Continuous IV infusion of morphine cannot be considered safe outside the recovery room or intensive care unit. The short duration of effect of meperidine and morphine demands six to eight intramuscular injections per day to control severe postoperative pain. Thus an analgesic with a longer duration of action could be advantageous in children. Single doses of intramuscular buprenorphine have been used in children for postoperative analgesia (8) and have been compared with caudal analgesia after circumcision (9). Sublingual buprenorphine has been used as premedication for children undergoing adenoidectomy and/or tonsillectomy (10). There are also preliminary reports on the use of buprenorphine for cancer pain in children (11). Generally buprenorphine has been accepted well and

the incidence of unwanted effects has been low except after circumcision, in which case 52% of the buprenorphine patients vomited (9). Postoperatively as well as when used for management of cancer pain the impression has developed that buprenorphine has a long duration of action. However, when buprenorphine was given intravenously by titration for 24 hours after thoracotomy, it did not have a longer duration of action than did morphine (3).

The randomization performed by the pharmacy of the Helsinki University Central Hospital did not result in equal distribution of the sexes of the children in the two groups in this study. Although there are some reports on different coping strategies for dealing with pain in boys and girls (12), we have not been able to show differences in the quantity or complaints of pain between Finnish boys and girls participating in our earlier analgesic studies (6).

Assessing children's pain poses more problems than does pain assessment in adults (13). The developmental state of young children does not permit them to express their suffering verbally. In all age groups children regress when they are hospitalized and are confronted with severe postoperative pain. They may refuse to speak and they only cry until a reasonable amount of pain relief has been given. Although children in the present study were well prepared for the operation and the analgesic study, their cooperation often failed in the recovery room. Therefore, we found it necessary to develop a reliable method for clinical observation of children in acute pain. It has been shown to correlate well with the child's own comments in all age groups (6). In the present study half of the patients fell asleep during the initial titration to complete analgesia and could not give their personal comment until later.

In the recovery room both treatments in the present study provided effective analgesia with a rapid onset of action when given intravenously. The potency ratio of buprenorphine to morphine 31.5:1, the longer duration of effect of the initial analgesic dose together with total drug consumption during the first 2 hours in the recovery room agree with the results of Tigerstedt and Tammisto (14). It is not always possible to distinguish sedation from analgesia when observing children. Thus the greater sedative effect of buprenorphine might have been mistaken for analgesia in children who fell asleep.

Low respiratory rates have been reported after the use of buprenorphine (3,8,14,15). Tidal volume, however, is usually large and the clinical picture is not generally judged to represent significant ventilatory depression. A typical feature is the slow decrease of the ventilatory rate over hours. Watson et al. (16) did



Table 5. Body Temperature (°C) During the Study Period by Treatment Group

	Evening of the operation	First postoperative day		Second postoperative day		Third postoperative day
		Morning	Evening	Morning	Evening	Morning
Buprenorphine	37.4 ± 0.8	37.3 ± 0.5	37.7 ± 0.6	37.4 ± 0.6	37.4 ± 0.6	36.9 ± 0.6
Morphine	37.5 ± 0.7	37.6 ± 0.5*	38.1 ± 0.5†	37.5 ± 0.7	37.7 ± 0.7	37.1 ± 0.6

Results are mean ± SD.

Compared to buprenorphine group (Student's *t*-test), \**P* = 0.019; †*P* = 0.012.

not see any reduction toward normal levels of arterial  $PCO_2$  for 3 hours after single IV doses of buprenorphine comparable to those used in this study for titration to complete initial analgesia. It is important to be aware of the danger of delayed ventilatory depression, especially in association with use of parenteral buprenorphine (3,15). Postoperative pulmonary function measurements did not differ between patients using 6-hourly sublingual buprenorphine or intramuscular morphine (17).

The long duration of action of buprenorphine documented in some adult studies (14,16,17) could not be demonstrated with the sublingual dosing on the ward in this study. In both study groups there were children who needed an analgesic every 4 to 5 hours. This agrees with the results reported by Risbo et al. in adult orthopedic patients (5). As a partial narcotic agonist buprenorphine has a ceiling effect that might be reached with the severe pain after extensive orthopedic surgery. Children generally expect the medication to abolish pain completely. If this does not happen, they consider the analgesia inadequate and ask for an additional dose. It has been shown that after sublingual buprenorphine, peak blood concentrations and analgesic effect are reached slowly in 2 to 3 hours (17). When the effect starts late the child probably does not associate the pain relief with the analgesic tablet. It is important to give a tablet to a child early when the pain starts. It might be advantageous to give sublingual buprenorphine prophylactically. However, this might lead to drowsiness and ventilatory depression in some patients because of the large individual variation in the need of narcotic analgesics (3,15).

In this study the potency ratio of sublingual buprenorphine to intramuscular morphine was consistently around 25:1, which is considerably lower than the ratio of the intravenous drugs in this and in our previous study (3). Together with the daily drug consumption it agrees well with the ratio of sublingual buprenorphine to intramuscular morphine given for pain after cholecystectomy in adults (4).

The incidence of unwanted side effects in the present study was low but qualitatively similar to

those reported in adult studies and was the same with both drugs. Nausea was not considered to be a problem because it was transient except in one child receiving buprenorphine, who was nauseated throughout the whole study period. Nausea was not associated with high doses of morphine or buprenorphine.

Twenty percent of the children participating in the study had difficulty in voiding and/or urinary retention for several days or throughout the study period. Most of them had to be catheterized. Every patient with urine retention had had high daily doses of buprenorphine or morphine ( $\geq 24.4$  or  $670 \mu\text{g/kg}$  on the first and second days,  $21.3$  or  $600 \mu\text{g/kg}$  on the third day, respectively). To avoid this kind of complication, it might be advantageous to combine anti-inflammatory analgesic agents with narcotics for orthopedic postoperative analgesia instead of increasing the narcotic dose (18).

Antipyretics were administered significantly more often to children given morphine than in those given buprenorphine. The medical background or the operations performed cannot explain the higher incidence of fever in the morphine group. Sweating reduces body temperature but sweating has not been reported to be more common with buprenorphine than with morphine (14,17), and was not reported in any patient in this series. The greater sedative effect of buprenorphine could contribute to maintaining the low body temperature. We are not familiar with reports on the effects of buprenorphine on thermoregulation. Although it has been shown that anti-inflammatory agents given regularly significantly improve postoperative analgesia (18), single doses of antipyretics probably have not markedly influenced the evaluation of the analgesic effects of the drugs used in the present study.

On the surgical ward 18/28 and 21/32 of the children given buprenorphine or morphine assessed the analgesic treatments to be "good" or "very good" on each day of the study with no significant differences between treatments. Why children did not consider the analgesic therapy good included insufficient or too brief analgesic effects and reluctance to accept

frequent injections. One patient in both treatment groups was withdrawn because of fear of injections. One patient given morphine and three given buprenorphine were withdrawn from the study because of insufficient analgesic effect. Not more than three children given buprenorphine regarded the therapy only satisfactory because of unwanted effects. Probably the children could not always associate unwanted effects with the analgesic treatment. Unwanted effects seem to have influenced the nurses' scores more often than the children's scores.

Overall this study showed that both of the methods for treatment that were studied provided safe and effective analgesia for children after orthopedic surgery. There were no clinically important differences between the two treatment regimes studied. Given the equality of effectiveness of both drugs, the principal consideration becomes, the route by which drugs are given for relief of postoperative pain. The present work demonstrates that after initial intravenous titration of analgesia in recovery, patients could then be maintained equally on either morphine by injection or buprenorphine using sublingual tablets. Injections are often an inconvenience to nursing staff and they are usually disliked, and occasionally refused, by children. Sublingual buprenorphine therefore appears to represent an appropriate alternative to morphine injection.

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## Interactions of Vecuronium and Atracurium in an In Vitro Nerve-Muscle Preparation

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VAN DER SPEK AFL, ZUPAN JT, POLLARD BJ, SCHORK MA. Interactions of vecuronium and atracurium in an in vitro nerve-muscle preparation. *Anesth Analg* 1988;67:240-6.

*Atracurium and vecuronium were compared when given alone and in combination in the in vitro rat phrenic nerve-hemidiaphragm preparation stimulated via the phrenic nerve. The slopes of the log dose response curves of atracurium and vecuronium were parallel; their ED<sub>50</sub>s were  $1.12 \pm 0.0035 \cdot 10^{-5}$  M and  $5.89 \pm 0.16 \cdot 10^{-6}$  M, respectively. The combination's log dose response curves were significantly shifted to the left when compared with those of either relaxant alone; an increased potency is displayed by the combination. These observations indicate nondepolariz-*

*ing muscle relaxant synergy for the combination of equal proportions of vecuronium and atracurium. The synergistic interaction of vecuronium and atracurium in this in vitro-model is not dependent on pharmacokinetic factors such as uptake, distribution, and biodegradation as are present in the in vivo animal models and in humans. Synergy of vecuronium and atracurium in vitro is a new finding and is consistent with hypotheses of multiple receptor sites and different modes of action of the "competitive" neuromuscular blocking agents. This degree of synergy, seen in the in vitro animal data, if extrapolatable to humans, is probably of little clinical significance.*

Key Words: NEUROMUSCULAR RELAXANTS—  
vecuronium, atracurium.

A number of studies indicate deviations from the predicted behavior of competitive neuromuscular blocking agents when administered alone or in combination (1-3). Based on the assumption that competitive kinetics are applied at a single receptor site, two neuromuscular blocking agents when mixed should interact in an additive manner (3). However, nondepolarizing muscle relaxant synergy has been demonstrated in vivo and in vitro for combinations of equal proportions of pancuronium and *d*-tubocurarine or pancuronium and metocurine (1-3). This synergy is consistent with hypotheses of multiple receptor sites and different intrinsic activity of the neuromuscular blockers at the neuromuscular junction (2,4). Results of the two in vivo studies on the effects of combinations of vecuronium and atracurium have been contradictory (5,6). Synergy was demonstrated for their

combinations in humans (5), whereas no evidence for relaxant synergy was found in the in vivo rat model (6). Combinations of atracurium and vecuronium have not been studied in an in vitro model, which precludes a number of pharmacokinetic factors present in vivo models. We investigated, therefore, the relaxant effects of atracurium and vecuronium, and those of their combination, in equal proportions, in the in vitro isolated phrenic nerve-hemidiaphragm preparation (7). Because of the presumed stereochemical similarity of vecuronium to pancuronium (8) and the potential stereochemical similarity of atracurium to metocurine (9), it appeared attractive to test the hypothesis that a combination of vecuronium and atracurium could produce synergy in the rat phrenic nerve-hemidiaphragm model.

### Materials and Methods

Sprague-Dawley rats, weighing between 180 and 230 g, were decapitated and the left hemidiaphragms with 3 cm of their accompanying phrenic nerves were dissected and transferred to Petri dishes containing oxygenated Krebs solution at room temperature. The

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thoracic wall was closely trimmed to the insertion of the diaphragm, which created a 1.5-cm wide base. The preparations were attached to carrier assemblies with stainless steel hooks through their bases and nonstretchable suture material through their central tendon, which was connected to an isometric force transducer (Harvard Bioscience, Natick, MA). The preparations were placed in identical organ baths of 50-ml capacity containing a modified Krebs solution aerated vigorously with carbogen (5% carbon dioxide in 95% oxygen) and maintained at 36–36.5°C. The electrolyte composition, in mM L, was:  $\text{Na}^+$  143,  $\text{Cl}^-$  129,  $\text{K}^+$  5.9,  $\text{Ca}^{2+}$  3.3,  $\text{Mg}^{2+}$  1.2,  $\text{HCO}_3^-$  25,  $\text{H}_2\text{SO}_4^{2-}$  1.2,  $\text{H}_2\text{PO}_4^-$  1.2, glucose 11.1. The partial pressures of oxygen ( $\text{Po}_2$ ), carbon dioxide ( $\text{Pco}_2$ ), and the electrolyte values were measured at least once during each experiment. The  $\text{Pco}_2$ , the pH, and the  $\text{Po}_2$  values ranged from 30–40 mm Hg, 7.32–7.40 and 640–690 mm Hg, respectively. Preceding the mounting of the preparations on the transducers, a two-point calibration with static loads was performed. Basal muscle tension was maintained at 2 g. The hemidiaphragms were stimulated indirectly with a Grass S88 stimulator (Grass Instruments Co., Quincy, MA), using supramaximal square wave stimuli of 0.2 msec duration at a frequency of 0.15 Hz. The resultant muscle force (twitch) was isometrically transduced through capacitance semiconductor transducers (Harvard Bioscience, South Natick, MA) and recorded on a Gould Brush 2400 recorder (Gould Instruments, Inc., Cleveland, OH).

Each preparation was allowed to stabilize for at least 30 minutes until a stable twitch height resulted. Adjustments to basal muscle tension were made before the administration of each relaxant dose. Thereafter, the preparations were again allowed to stabilize before the muscle relaxant was administered. We rejected preparations that failed to develop a minimum of 20 g force at a basal tension of 2 g. All preparations were pretreated with a mixture of vecuronium and atracurium before the start of the single dose-response curves (SDRC). Pretreatment of this *in vitro* preparation reduces the variability of response to the subsequently administered relaxant (especially the response to the first dose); it results in a greater predictability of the subsequent responses. Three wash periods of 5 minutes preceded each dose administration. The relaxants were administered from precision microliter syringes (Hamilton, Co., Reno, Nevada) to a maximum of 146  $\mu\text{L}$ , so that the final volume of the bath changed by no more than 0.3%. Stock solutions were prepared from the commercially available preparations (vecuronium: Organon Inc, West Orange, NJ; atracurium: Burroughs-Wellcome,

Chapel Hill, NC) and were stored at 4°C before and during the experiments. Final dilutions were prepared using double deionized water just before each experiment.

### *Experimental Design*

The experiment consisted of two parts. Part one served to establish an equipotent basis for comparison, the dose equivalent unit or DU. The dose equivalent unit permits the construction of dose response curves in DUs of relaxants with dissimilar absolute dose response curves and thereby allows for comparisons of these dissimilar relaxants on the same arbitrary scale. Three SDRCs per preparation were constructed for each relaxant. This procedure was repeated on six different preparations for each relaxant. Each SDRC consisted of three doses which were preceded by three wash periods of 5 minutes and basal tension adjustment as described above. Preliminary experiments showed minimal accumulation of the drug with this wash-out technique. The maximum stable depression of twitch height after a dose is expressed as a percentage reduction of the twitch height immediately preceding that dose. The maximum depression was usually reached after 5–10 minutes and was present for at least 1 minute before the measurement took place. The concentration required to depress twitch height by 50%, the  $\text{ED}_{50}$ , was calculated for each SDRC from linear regression analysis. The 18  $\text{ED}_{50}$ s (six preparations times three replicates per preparation) of the SDRCs for each relaxant were averaged and were defined as one dose equivalent unit or one DU for that relaxant.

In the second part of the experiment, three SDRCs on each preparation were constructed, one for vecuronium, one for atracurium, and one for their combination. The nerve diaphragm preparations were pretreated, washed, and allowed to stabilize as described above. Then for each preparation, the SDRCs, in DU, to atracurium, vecuronium, and their combination, in equal proportion, were constructed. Each SDRC consisted of three doses in the range of 0.5 to 1.65 DU of each relaxant or their combination. Equal proportions of vecuronium and atracurium (in DU) were administered simultaneously to the bath to arrive at the appropriate dose range of the combination in DU. Three 5-minute wash periods and basal tension adjustment preceded each dose. The order of the respective relaxants (vecuronium, atracurium, or their combination) and the dose levels (a high, intermediate, and low dose) were randomized for a total of 18 test preparations. The stable depression of twitch



height after a dose is expressed as before and it was usually reached after 5–10 minutes and lasted at least 1 minute before measurement.

### Statistical Analysis

The  $ED_{50}$ s, slopes and the coefficients of determination ( $R^2$ ) of the log dose-response curves were calculated from linear regression analysis on the basis of the three responses between 20 and 80% twitch height depression for atracurium, vecuronium, and their combination (10). The same analysis was used to derive the overall  $ED_{50}$ s in the preliminary experiment to establish the dose equivalent unit. The intrapreparation  $ED_{50}$ s and slopes of the SDRCs of atracurium, vecuronium, and their combination in the second part of this study were compared using repeated measures analysis of variance (RM-ANOVA) (11). This analysis is used to compare the effects of three (or more) treatments (relaxants) for the responses (twitch) of the same experimental subject (12). The RM-ANOVA produces an overall  $F$ -statistic for which the significance is reported. Furthermore, pairwise multiple comparisons (Scheffe) between the treatment groups report which of the three treatments (atracurium, vecuronium, and their combination) differ significantly from one another. Using the RM-ANOVA, the effects of experimental and biological variation between preparations are reduced by intrapreparation comparisons within the treatment group.

Vecuronium, atracurium, and the combination were presented in three possible positions of order (that is the first, second, or third SDRC on a preparation) in the 18 different preparations. The effects of order on the  $ED_{50}$ s and slopes of the individual relaxants were evaluated by interpreparation comparison using analysis of variance (ANOVA). When multiple comparisons were made, Scheffe's correction was applied. The coefficients of variation of the  $ED_{50}$ s were calculated for each relaxant in each order.

### Results

The first part of the experiment served to establish the overall  $ED_{50}$ s for vecuronium and atracurium; these were  $5.89 \pm 0.16 \cdot 10^{-6}$  M and  $1.12 \pm 0.0035 \cdot 10^{-5}$  M, respectively. The  $ED_{50}$ s served as the equipotent dose equivalent units (DU), the basis for comparison of atracurium and vecuronium in the second part of the experiment.

Table 1. Mean  $ED_{50}$ s, Slopes, and  $R^2$  of the Dose-Response Curves for Atracurium, Vecuronium, and their Combination on 18 Preparations

Relaxant	$ED_{50} \pm SE$	Slope $\pm SE$	$R^2$
Vecuronium	$1.07 \pm 0.03$	$187 \pm 9$	0.97
Atracurium	$1.07 \pm 0.04$	$188 \pm 11$	0.97
Combination	$0.97 \pm 0.03^*$	$185 \pm 8$	0.95

\*Repeated measures analysis of variance indicated an overall significant ( $P < 0.01$ ) difference with a  $F$  test of 5.0. Pairwise comparison (Scheffe) demonstrated a significant difference ( $P < 0.04$ ) between  $ED_{50}$ s of combination and those of atracurium and vecuronium. The mean slopes among the three relaxants did not differ significantly.

The results of the second part are listed in Tables 1 and 2. A graphic summary indicates the mean dose response lines for the 18 SDRCs of vecuronium, atracurium, and their combination on the 18 preparations, see Figure 1. The results can be summarized as follows. The fits of the regression lines for the SDRCs had mean coefficients of determination ( $R^2$ ) for atracurium of 0.98 (range 0.81 to 0.99), for vecuronium of 0.98 (range 0.87 to 0.99), and for the combination of 0.96 (range 0.75 to 0.99). The result of the RM-ANOVA of the slopes demonstrated an overall insignificant  $F$  statistic, i.e., no significant differences among the slopes of atracurium, vecuronium, or their combination, were observed. The RM-ANOVA of the  $ED_{50}$ s indicated an overall significant ( $P < 0.01$ )  $F$  statistic. Pairwise multiple comparisons (Scheffe) demonstrated that the  $ED_{50}$ s of vecuronium and atracurium did not differ significantly ( $P < 0.05$ ), but that the  $ED_{50}$ s of atracurium and vecuronium each differed from the  $ED_{50}$ s of the combination ( $P < 0.04$ ). The SDRCs of the combination of vecuronium and atracurium demonstrated a shift to the left in a parallel fashion; thus the combination is more "potent" than expected on the basis of either relaxant alone when administered in the same equipotent DUs.

Analysis of variance of the  $ED_{50}$ s of the individual muscle relaxant demonstrates that from the first to the third order, the mean  $ED_{50}$ s decreased for all drugs. However, it was only in the case of vecuronium that a significant reduction was obtained from the first order exposures to those of the second and third order, ( $P < 0.03$  and  $< 0.01$ , respectively). The results are listed in Table 2. The slopes of the SDRCs of vecuronium, atracurium, and their combination did not change significantly with order (ANOVA). The coefficients of variation of the  $ED_{50}$ s ranged from 8 to 12% in the first, from 11 to 12% in the second, and from 8 to 13% in the third SDRC.

Table 2. Results of the ANOVA of Order on the ED<sub>50</sub>s for Vecuronium, Atracurium, and their Combination

	Muscle relaxant				F test
	1st Order (ED <sub>50</sub> ± SE)	2nd Order (ED <sub>50</sub> ± SE)	3rd Order (ED <sub>50</sub> ± SE)	Overall P value	
Vecuronium	1.21 ± 0.05	1.02 ± 0.05	0.98 ± 0.08	0.005	7.8*
Atracurium	1.19 ± 0.06	1.03 ± 0.05	0.99 ± 0.05	0.06	3.5
Combination	1.02 ± 0.04	1.00 ± 0.05	0.90 ± 0.04	0.16	2.0

\*By pairwise multiple comparisons according to Scheffe's method, the 1st order exposures differed significantly from those in the 2nd and 3rd order at the 97 and 99% level, respectively. There are six preparations per relaxant for each order.

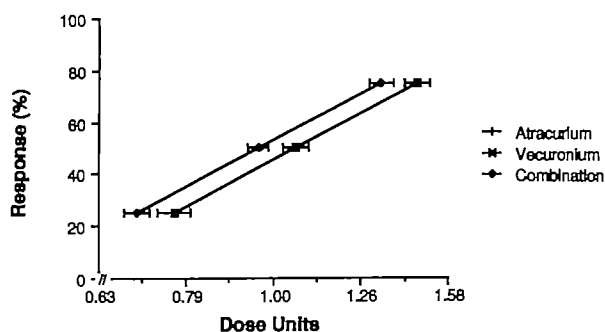


Figure 1. Graphic summary of the mean single dose-response curves for vecuronium, atracurium, and their combination is displayed for the responses between 20 and 80% twitch depression. The percentage depression of twitch height (as a fraction of control twitch height) is given on the ordinate. The log-dose, given in dose units, is plotted on the abscissa. The mean standard errors for three response points of the 18 single dose-response curves for each relaxant and their combination are displayed. The ED<sub>50</sub>s of the combination are significantly different ( $P < 0.04$ ) from those of vecuronium and atracurium as determined by pairwise comparisons. There is a shift to the left of the dose response curves for the combination, i.e., synergy is displayed. The slopes of the dose-response curves of vecuronium and atracurium are not significantly different. The dose response curves of atracurium and vecuronium overlap.

## Discussion

The results of this study demonstrated nondepolarizing muscle relaxant synergy for the combination of vecuronium and atracurium, when combined in equal equipotent proportions in an in vitro nerve muscle preparation at low rates of stimulation. Synergy of the combination of vecuronium and atracurium in an in vitro model is a heretofore unreported finding. Synergy of a combination is defined as a response to the combination that is more than expected on the basis of the sum of the presumed equipotent doses of the individual muscle relaxants (3). Nondepolarizing relaxant synergy has previously been demonstrated for pancuronium, alcuronium, and gallamine when combined with either *d*-tubocurarine or metocurine in vivo and in vitro (1,2,3,13,14). Vecuronium bromide, a pancuronium analog, has an affinity for the postjunctional receptors similar to that of pancuronium (8). Recently, distinct prejunctional receptor effects have also been demonstrated for

vecuronium (15). Stereochemically, vecuronium is closely related to pancuronium; however, it is unstable at physiologic pH at 36.5°C and undergoes metabolic conversion to relatively inactive metabolites (16). Like pancuronium, vecuronium displays synergy when combined with *d*-tubocurarine in humans (17), whereas it shows additivity in combination with pancuronium (18). Atracurium's structure is of a unique class (19). It is unstable under conditions of physiologic pH and temperature and undergoes spontaneous degradation (20). Stereochemically, its conformational state may resemble that of metocurine (9). Atracurium's action in the neuromuscular junction is probably predominantly at the postjunctional receptor complex with little nerve terminal effects (21).

Combinations of atracurium and vecuronium in in vivo models either produced no evidence for deviations from additivity in the rat (6) or demonstrated synergy in humans (5). Black et al. (5) studied combinations of atracurium and vecuronium of different equipotent doses (ED<sub>20</sub>s, -<sub>40</sub>s, -<sub>60</sub>s, -<sub>80</sub>s) in healthy humans about to undergo elective surgery. Using a single dose-response technique and the evoked electromyogram (EMG) as an indicator of neuromuscular blockade, they demonstrated nonparallel dose response curves for vecuronium and atracurium as well as synergy for the equipotent combinations of vecuronium and atracurium, except for the estimated ED<sub>80</sub>s, which did not reach statistical significance. Demonstration of synergy for the combinations of vecuronium and atracurium in our in vitro model is in agreement with the findings of Black et al. (5). An inspection of the slopes of the SDRCs of vecuronium and atracurium in this in vitro model, however, demonstrates no significant differences among them. Discrepancies between the in vivo human study by Black et al. and this in vitro study may be due in part to different methodology and analysis in addition to the different experimental subjects used. Quantization of the relaxant effect in the human study was achieved using the evoked EMG technique as opposed to the evoked muscle twitch technique. In their

study, one relaxant dose-response was obtained per human subject, whereas repeated single dose-responses for both relaxants and their combination were obtained in each nerve muscle preparation in the present study. The latter approach permits intra-subject comparisons versus intersubject comparisons in the human study.

Synergy of vecuronium and atracurium in this in vitro rat phrenic nerve hemidiaphragm model is in contrast with the findings of Booij et al. (6). They demonstrated additivity and parallel dose-response curves for all the relaxant combinations tested including pancuronium, *d*-tubocurarine, vecuronium, and atracurium. In their in vivo rat sciatic nerve tibialis muscle model, cumulative dose-response curves were constructed using indirectly stimulated muscle twitches to quantify relaxation. Additional cumulative doses of the relaxants were administered after only two consecutive twitches had the same reduced height. Lack of a steady state of the relaxants at the neuromuscular junction may result in underestimating the relaxant effect as well as the presence and degree of synergy or antagonism. The same experimental procedure was followed for all relaxants, regardless of differences in degradation of the respective relaxants over time as illustrated by the difference in stability between pancuronium and atracurium. Further differences with the current study may stem from the construction of one cumulative dose response curve per subject and subsequent interanimal comparisons. Using the one-way analysis of variance, differences in drug effect may not be detected in a small number of experiments due to interanimal variation. Dose-response relations were calculated using the "normal probability integral" model which includes the 100% response points, whereas linear regression analysis of the responses between 20 and 80% was used in the current study (22,10). Inclusion of the 100% response points may cause generally flattened dose-response curves with nondistinct slopes. Isobolograms were constructed from calculated (rather than measured) values derived from few experiments, thus potentially underestimating deviations from the isoboles (23). Their findings are at variance with a number of other studies. For example, synergy for the combination of pancuronium and *d*-tubocurarine has consistently been demonstrated in vivo and in vitro in different animals as well as in humans (1-3). Further discrepancies may have arisen from the type of preparation (sciatic nerve-tibialis or ulnar nerve-hypothenar muscle versus phrenic nerve-hemidiaphragm) and the type of experiment (in vivo versus in vitro). The in vivo models include pharmacokinetic considerations of the intact subjects

such as uptake, distribution, nonspecific binding, and (bio-) degradation of the relaxants. The isolated nerve-muscle preparation excludes a number of these pharmacokinetic considerations.

The presence of synergy in this in vitro neuromuscular preparation provides further evidence against differences in competitive nonspecific protein binding (24) or alterations in tissue blood flow (14) as the predominant factors responsible for the observed synergy in the in vivo models. (Bio-)degradation of vecuronium and atracurium at physiologic pH and temperature occurs in the muscle bath; however, this is unlikely to lead to the synergistic effect. Pharmacokinetic factors such as the potentially different diffusion rates of atracurium and vecuronium in the synaptic cleft or differences in affinity and dissociation constants cannot be excluded in this model. However, these (sub-) synaptic pharmacokinetic factors can be assessed by voltage clamp techniques of the neuromuscular junction (25), while their influence can be described and predicted by computer models (25,26). Antagonism of neuromuscular blocking agents has been postulated in the presence of one postjunctional receptor type (27). When acetylcholine receptor ligands with greatly differing affinities such as hexamethonium and *d*-tubocurarine are present, antagonism of their combinations can be demonstrated (25). It is assumed in the latter model that each postjunctional receptor channel is controlled by two acetylcholine receptor sites, both of which need to be occupied simultaneously with acetylcholine molecules for the channel to be fully functional (25). A synergistic effect of two neuromuscular blocking agents of similar affinities, administered in equipotent doses, has not yet been demonstrated in this system of one type of postjunctional receptor.

The classical view of neuromuscular transmission holds that the failure of transmission in the presence of "competitive" neuromuscular blocking agents occurs by the selective occupation of the acetylcholine receptors located at the end plate region of the muscle membrane (28). Synergy of atracurium and vecuronium in this model is a deviation from simple competitive kinetic interactions at a single receptor site (3). We interpret the synergistic interactions of vecuronium and atracurium to be consistent with theories of multiple receptor sites and different intrinsic activities of the nondepolarizing neuromuscular blocking agents. Potential sites include pre- and postjunctional acetylcholine receptors (29,30) and their ionic channels (31). Differences in receptor and channel blocking capabilities have not yet been demonstrated for atracurium and vecuronium. Vecuronium and/or atracurium may modulate the mobilization and re-



lease of acetylcholine by acting on the nerve terminal membrane akin to the postulated actions of *d*-tubocurarine (32). The recent demonstration of prejunctional effects of vecuronium (15), the relatively minor prejunctional effects of atracurium (21), and the observation of nondepolarizing relaxant synergy in this study are consistent with and support hypotheses of multiple receptor sites. The contribution of the nonclassical sites to neuromuscular transmission and neuromuscular blockade in vivo is unknown. These sites, however, are proposed to be active during neuromuscular transmission at physiologic rates of stimulation and are implicated in the inhibition of neuromuscular transmission by the competitive neuromuscular inhibitors (30). The results of this study are consistent with these hypotheses.

The order of exposure represents the effects of metabolic and mechanical changes of the preparation over time, drug carry-over, preceding drug exposure, etc. and, therefore, it may significantly affect the ED<sub>50</sub>s, slopes, or other parameters of the experiment. The lack of a significant order effect on the ED<sub>50</sub>s of atracurium and the combination is, in part, probably due to the randomized single dose-response design as opposed to a cumulative design as used by Waud et al. (3). Pretreatment of an in vitro preparation reduces the variability of response to the subsequent administration of the relaxant (especially the first dose) and results in a greater predictability of the response. The consistent coefficients of variation support this observation. However, pretreatment may alter other characteristics of the preparations or drugs under study, e.g., if one were to study the interanimal variability of response to a single dose of drug this method may underestimate such variability.

From a clinical point of view, the anesthesiologist has to be able to decide whether there is an advantage in the use of the combination of atracurium and vecuronium. If significant synergy were present, then relatively small amounts of the combination of both agents could lead to a more profound neuromuscular blockade than expected on the basis of either agent alone. A reduction of the potential dose-related side effects, as has been demonstrated for the combinations of metocurine and pancuronium, could thus be achieved (33). Another potential benefit of this synergistic combination may be a reduction in the duration of the block when compared with the duration of equipotent doses of either agent alone. The degree of synergy displayed by the combination of atracurium and vecuronium in this in vitro model appears to be of a lesser magnitude than that demonstrated by combinations of pancuronium with metocurine or pancuronium with *d*-tubocurarine in sim-

ilar in vitro models (2,3). Although one needs to exercise great caution when extrapolating in vitro animal data to humans, the current in vitro data suggest the potential for a small degree of synergy for the combination of atracurium and vecuronium in humans. In fact, from their human data, Black et al. (5) suggest that a combination of low doses of atracurium and vecuronium may lead to a significant increase in neuromuscular blockade.

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## Ventilatory Responses to Hypercapnia during Bupivacaine Spinal Anesthesia

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Ventilatory responses to hypercapnia during bupivacaine spinal anesthesia. *Anesth Analg* 1988;67:247-52.

*The effect of spinal anesthesia with isobaric 0.5% bupivacaine on ventilatory responsiveness to CO<sub>2</sub> rebreathing was studied in ten unpremedicated patients. Minute ventilation ( $\dot{V}_E$ ) at end-tidal  $P_{CO_2} = 55$  mm Hg increased from  $18.7 \pm 6.7$  L/min (mean  $\pm$  SD) to  $22.3 \pm 10.1$  L/min after induction of spinal anesthesia ( $P < 0.05$ ). Occlusion pressure ( $P_{0.1}$ ) at  $P_{CO_2} = 55$  mm Hg also increased, from*

*$3.8 \pm 1.5$  to  $5.0 \pm 1.7$  cm H<sub>2</sub>O ( $P < 0.05$ ). Spinal anesthesia was not associated with significant changes in vital capacity, maximal inspiratory pressure, resting end-tidal  $P_{CO_2}$ , or the slopes or intercepts of the lines relating  $\dot{V}_E$  or  $P_{0.1}$  to  $P_{CO_2}$ . These results show an increased ventilatory responsiveness to CO<sub>2</sub> with bupivacaine spinal anesthesia.*

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHETICS, LOCAL—bupivacaine. VENTILATION—carbon dioxide response.

Patients sometimes report difficulty breathing during spinal anesthesia, despite adequate inspiratory muscle function. Such complaints suggest an altered drive to breathe; nevertheless, spinal anesthesia is thought to have no significant effect on resting pulmonary ventilation (1).

Measuring ventilatory responses to CO<sub>2</sub> rebreathing provides a more sensitive method to detect changes in the control of breathing than does measuring changes in resting ventilation. Hypercapnia is a potent stimulus to ventilation; relatively small changes in ventilatory responses to progressive hypercapnia may be more readily quantified than the corresponding changes in resting ventilation. We therefore studied ventilatory responses to CO<sub>2</sub> rebreathing as a measure of change in control of breathing in patients during spinal anesthesia.

### Methods

Ten subjects, free of clinically significant cardiac or pulmonary disease, were studied. All were scheduled

for knee or foot surgery and had agreed to have spinal anesthesia. The protocol was approved by the Human Subjects Committee of our institution. Written informed consent was obtained from each subject.

### Protocol

Subjects were fasted overnight and received no preoperative medications. Baseline (prespinal) measurements were performed in the preoperative holding area, 1–2 hours before operation. Two or three measurements were made of each of the following: 1) maximal inspiratory pressure (MIP), 2) forced vital capacity (VC) and, 3) ventilatory response to CO<sub>2</sub> rebreathing.

Spinal anesthesia was administered in the operating room with 0.5% bupivacaine without dextrose (isobaric). The dose of bupivacaine, the addition of epinephrine to bupivacaine, and the position of the patient during injection were at the discretion of the anesthesiologist performing the procedure. Hypotension was treated with IV ephedrine. The level of spinal anesthesia to pinprick was assessed every 5 minutes. When the level was unchanged on two successive determinations, all respiratory measurements were repeated in duplicate.

### Respiratory Measurements

All measurements were made with the subjects supine, their head supported by one or two pillows.

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The first subject breathed through a rubber mouthpiece while wearing a nose-clip, which she found uncomfortable; consequently, all other subjects breathed through plastic face masks which sealed around the nose and mouth.

MIP was measured at residual lung volume. For this measurement, the mouthpiece or face mask was attached to one end of a short length (10 cm) of 2.5-cm diameter rigid pipe, the other end of which could be manually occluded. Pressure within the pipe was determined with a differential pressure transducer (model LCVR, range  $\pm 200$  cm H<sub>2</sub>O, Celesco Transducer Products, Inc., Canoga Park, CA) and recorded on a strip-chart recorder (model 8000S, Gould Inc., Cleveland, OH). The pressure transducer was calibrated with a water manometer before each experiment. MIP was determined as the maximal pressure deviation from atmospheric observed during two or three efforts under each condition.

Forced vital capacity was measured using a Wedge spirometer (model 570, Med Science, St. Louis, MO). The volume signal of the spirometer was verified initially with a calibrated syringe; daily electrical calibration was performed. Forced vital capacity was determined as the maximal volume exhaled during repeated attempts, and was converted to BTPS.

Ventilatory response to CO<sub>2</sub> rebreathing was tested by the rebreathing method of Read (2). Subjects breathed through a nonrebreathing valve (model 2700, Hans Rudolph, Inc., Kansas City, MO) connected via a circle system of tubing to a rebreathing bag enclosed in a rigid box. A three-way valve allowed subjects to breathe either air or a gas mixture from the bag. The box was connected to the spirometer for measurement of volume and flow. A silent inflatable occlusion valve (model 9327, Hans Rudolph, Inc.) on the inspiratory side of the circle system allowed measurements of mouth occlusion pressure. Intermittent inspiratory occlusion was performed by inflation of the valve during the previous expiration; the occlusion was terminated within 200–350 msec after onset of inspiration by deflation of the valve.

Prior to rebreathing, the bag was filled with 3 L of 7% CO<sub>2</sub>–93% O<sub>2</sub>. Each test started with the subject breathing air through the face mask or mouthpiece until end-tidal CO<sub>2</sub> partial pressure (P<sub>ETCO<sub>2</sub></sub>) appeared stable. The three-way valve was then turned, and the subject was instructed to take three quick deep breaths from the bag, and then to breathe normally. Rebreathing continued for 3 to 5 minutes, as tolerated. Inspiratory occlusion was performed once every 20 to 30 seconds during rebreathing.

Expired gas was sampled continuously at the

mouthpiece or mask at a rate of 500 ml/min. Concentration of CO<sub>2</sub> in expired gas was measured with an infrared analyzer (LB-2, Beckman Instruments, Inc., Anaheim, CA), which was calibrated before each experiment against room air and the rebreathing gas. Sampled gas was returned to the rebreathing bag after analysis. Breath-by-breath volume and flow were determined by the Wedge spirometer connected to the bag-in-box system. Pressure was measured by a transducer (Celesco model LCVR, range  $\pm 50$  cm H<sub>2</sub>O, calibrated daily) connected by 2-mm tubing to a sampling port just before the nonrebreathing valve. All signals were recorded continuously on the strip-chart recorder for subsequent analysis.

Resting P<sub>ETCO<sub>2</sub></sub> was determined by averaging the values from three to five breaths just before each rebreathing study. To relate minute ventilation ( $\dot{V}_E$ ) and P<sub>ETCO<sub>2</sub></sub> during rebreathing,  $\dot{V}_E$  was calculated at BTPS from the tidal volumes and total duration of three consecutive breaths immediately preceding each occluded breath. For the corresponding P<sub>ETCO<sub>2</sub></sub>, the mean value during each 3-breath interval was used. Data from the pair of rebreathing curves performed under each condition were pooled for calculation of the best-fit line by linear regression.

Mouth occlusion pressure (P<sub>0.1</sub>) was measured during each occlusion 100 msec after the beginning of an inspiratory effort, determined by the onset of a subatmospheric pressure deflection. The corresponding P<sub>ETCO<sub>2</sub></sub> was measured for the breath just before the inspiratory occlusion. Again, data from the pair of rebreathing studies done under each experimental condition were pooled for calculation of the best-fit line by linear regression relating P<sub>0.1</sub> and P<sub>ETCO<sub>2</sub></sub>.

The slope and x-intercept of each line, as well as the  $\dot{V}_E$  and P<sub>0.1</sub> calculated at P<sub>ETCO<sub>2</sub></sub> = 55 mm Hg, were used for comparison of results obtained before and after spinal anesthesia. Statistical significance was determined by Student's *t*-test for paired samples.

## Results

Patient characteristics and drug dosages are shown in Table 1. The level of anesthesia to pinprick was between T2 and T10 in all subjects at the time of respiratory measurements (Table 1).

There were no significant differences in VC (mean  $\pm$  SD, 2.5  $\pm$  1.1 before, 2.6  $\pm$  1.0 L during spinal) or MIP (41  $\pm$  20 before, 42  $\pm$  20 cm H<sub>2</sub>O during). Resting P<sub>ETCO<sub>2</sub></sub> was 40  $\pm$  3 mm Hg before spinal anesthesia and 38  $\pm$  3 mm Hg during spinal (*P* = 0.07) (Fig. 1).

Table 1. Patient Characteristics

Patient No.	Age (yr)*	Sex	Dose bupivacaine (mg)	Dose epinephrine (mg)	Dose ephedrine (mg)	Analgesic level
1	66	F	15	0	0	T9
2	70	M	15	0	0	T9
3	57	F	15	0	0	T4
4	29	M	20	0.1	0	T10
5	49	F	15	0	0	T10
6	74	F	15	0	15	T4
7	68	F	15	0	0	T10
8	62	F	15	0	0	T2
9	58	F	15	0.2	0	T2
10	76	M	15	0.2	5	T2

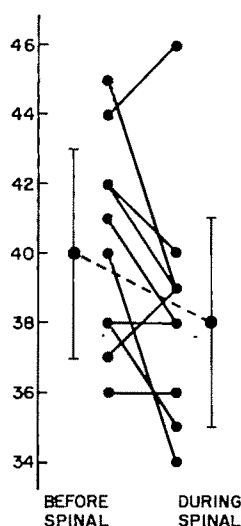
\*Mean  $\pm$  sd 61  $\pm$  14.

Figure 1. Resting end-tidal  $P_{CO_2}$  (mm Hg) before and during spinal anesthesia. The dashed line connects mean values. Error bars represent  $\pm 1$  sd.

There were no significant changes in slopes or x-intercepts of the lines relating  $\dot{V}_E$  and  $P_{0.1}$  to  $P_{ETCO_2}$  before and during spinal anesthesia (Table 2). However,  $\dot{V}_E$  calculated at  $P_{ETCO_2} = 55$  mm Hg ( $\dot{V}_{E-55}$ ) increased from  $18.7 \pm 6.7$  L/min (mean  $\pm$  sd) before spinal to  $22.3 \pm 10.1$  L/min during spinal ( $P = 0.04$ ) (Fig. 2). Similarly,  $P_{0.1}$  calculated at  $P_{ETCO_2} = 55$  mm Hg ( $P_{0.1-55}$ ) increased from  $3.8 \pm 1.5$  to  $5.0 \pm 1.7$  cm  $H_2O$  ( $P = 0.04$ ) (Fig. 3).

## Discussion

The major finding in the present study was an increase in the ventilatory response to  $CO_2$  rebreathing during bupivacaine spinal anesthesia in unpremedicated patients. The increased responsiveness was manifested by a 19% increase in  $\dot{V}_{E-55}$  and a 32%

increase in  $P_{0.1-55}$ . Eight of ten patients had increased  $\dot{V}_{E-55}$  (Fig. 2) and the same eight had increased  $P_{0.1-55}$  (Fig. 3), whereas there were no consistent changes in the slopes or x-intercepts of the lines relating  $\dot{V}_E$  and  $P_{0.1}$  to  $P_{ETCO_2}$ . Thus, there was a shift of the lines toward the left (increased response) with spinal anesthesia. Resting  $P_{ETCO_2}$  decreased in our patients from  $40 \pm 3$  to  $38 \pm 3$  mm Hg with spinal anesthesia, a statistically insignificant change ( $P = 0.07$ ).

Previous studies have found relatively little effect of spinal anesthesia on resting pulmonary ventilation. Egbert et al. (3) observed no significant changes in respiratory rate or tidal volume in 20 sedated patients with tetracaine sensory block to T2-T6. Askrog et al. (4) noted "slightly increased" minute ventilation with no change in tidal volume while arterial  $PCO_2$  decreased from  $35.8 \pm 1.4$  to  $32.3 \pm 3.1$  mm Hg in six sedated subjects with tetracaine sensory block to T4-T6. Pitkänen (5) observed no change in arterial  $PCO_2$  with bupivacaine spinal anesthesia in 40 sedated patients. Other studies reviewed by Greene (6) also reported little or no effect of spinal anesthesia on resting ventilation or  $P_{ETCO_2}$ . In many of these studies, subjects were sedated with drugs now known to affect control of breathing; effects of such sedative drugs may have masked any effect of spinal anesthesia.

Eisele et al. (7) found no change in minute ventilation with procaine spinal anesthesia producing motor block to level T1 in three subjects; tidal volumes were reduced while respiratory rate increased. These authors reported the ventilatory response to  $CO_2$  rebreathing in one of their subjects. Although they noted similar slopes of the minute ventilation- $P_{ETCO_2}$  relation before and after anesthesia, the data in their Figure 5 appear to show a shift of the response toward higher ventilation with spinal anesthesia, in agreement with our findings.

Table 2. Ventilatory Responses to CO<sub>2</sub> Rebreathing before and during Spinal Anesthesia

Patient no.	Minute ventilation ( $\dot{V}_E$ )				Occlusion pressure ( $P_{0.1}$ )			
	Slope (L·min <sup>-1</sup> ·mm Hg <sup>-1</sup> )		x-intercept (mm Hg)		Slope (cm H <sub>2</sub> O/mm Hg)		x-intercept (mm Hg)	
	Before	During	Before	During	Before	During	Before	During
1	1.2	1.2	41	40	0.48	*	47	*
2	1.5	2.2	42	49	0.40	0.22	45	39
3	0.8	0.7	39	32	0.20	0.25	46	35
4	1.7	2.3	39	41	0.32	0.49	39	39
5	2.7	1.8	45	36	0.13	0.54	23	41
6	1.1	0.6	45	30	0.13	0.21	42	40
7	0.7	1.2	37	43	0.19	0.23	39	38
8	0.8	0.5	39	25	0.21	0.11	38	17
9	2.3	2.4	42	38	0.26	0.16	39	27
10	1.3	1.9	38	44	0.71	0.23	46	30
Mean $\pm$ SD	1.4 $\pm$ 0.7	1.5 $\pm$ 0.7	41 $\pm$ 3	38 $\pm$ 7	0.30 $\pm$ 0.18	0.27 $\pm$ 0.15	40 $\pm$ 7	34 $\pm$ 8

\*Insufficient data.

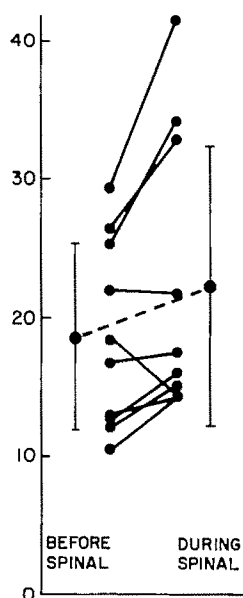


Figure 2. Minute ventilation (L/min) at end-tidal PCO<sub>2</sub> of 55 mm Hg, before and during spinal anesthesia. The dashed line connects mean values. Error bars represent  $\pm$  1 SD.

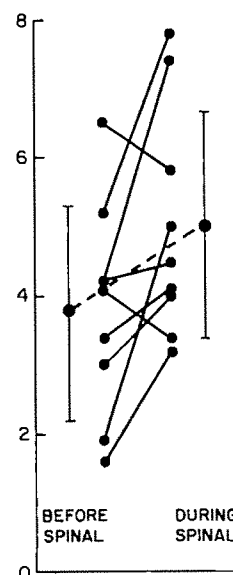


Figure 3. Occlusion pressure (cm H<sub>2</sub>O) at end-tidal PCO<sub>2</sub> of 55 mm Hg, before and during spinal anesthesia. The dashed line connects mean values. Error bars represent  $\pm$  1 SD.

Possible causes for the increased ventilatory responsiveness to CO<sub>2</sub> with spinal anesthesia in our patients include the following: 1) anxiety related to surgery, 2) systemic effects of bupivacaine, 3) systemic effects of sympathomimetics, 4) altered muscle function and, 5) altered afferent information. We will consider each of these in turn.

Without benefit of sedative drugs, some of our patients were anxious at being in the operating room during the postspinal measurements. The effect of such anxiety on CO<sub>2</sub> responsiveness is not known. The possibility that anxiety might increase ventilatory responses to CO<sub>2</sub> is suggested by studies that have shown that catecholamine infusions increase resting

ventilation (8,9) as well as responses to hypercapnia (10). On the other hand, lack of an effect of adrenergic blockade on resting ventilation or on ventilatory response to hypercapnia (11-13) argues against a significant role for sympathoadrenal activity in modulating CO<sub>2</sub> responsiveness. Because we did not study subjects having spinal anesthesia without impending surgery, we cannot exclude the possibility that anxiety related to surgery contributed to the increased CO<sub>2</sub> responsiveness we observed.

It is unlikely that systemic effects of bupivacaine contributed to the increased ventilatory responsiveness in our patients in view of the low blood levels of bupivacaine to be expected after subarachnoid ad-



ministration. Although ventilatory responsiveness to  $\text{CO}_2$  has been shown to be increased by bupivacaine administered by inhalation (14) and by axillary block (15), and by IV and epidural lidocaine (16,17), the magnitude of the increase in slope of the ventilatory response to  $\text{CO}_2$  correlated with plasma levels of local anesthetic (15,17). We did not measure plasma levels of bupivacaine in our patients; however, Axelsson et al. (18) found peak whole blood levels of 36–73 ng/ml following subarachnoid injection of 20 mg of glucose-free 0.5% bupivacaine. Such concentrations are more than an order of magnitude lower than the plasma bupivacaine levels of 1 and 3  $\mu\text{g/ml}$  at which Cross et al. (19) found no effect of IV bupivacaine on ventilatory response to  $\text{CO}_2$ . Similarly, in Negre's study (15), no change in slope of  $\dot{V}_E$  vs  $\text{PET}_{\text{CO}_2}$  was seen at plasma bupivacaine levels of  $<1 \mu\text{g/ml}$ .

Sympathomimetic drugs are known to increase resting ventilation (8,9) as well as ventilatory responsiveness to hypercapnia (10). Four of our patients received such drugs—epinephrine was added to bupivacaine in three patients and ephedrine was administered intravenously in two patients (one of whom had received epinephrine; see Table 1). Of those not receiving sympathomimetics,  $\dot{V}_E$ -55 and  $P_{0.1}$ -55 increased during spinal anesthesia in five of six patients. Thus, systemic effects of sympathomimetic drugs were not responsible for the increased ventilatory responsiveness during spinal anesthesia.

Also unlikely as a cause of increased responsiveness is altered ventilatory muscle function with spinal anesthesia. We observed no effect of bupivacaine spinal anesthesia on respiratory muscle function as measured by VC or MIP. The relatively low values of MIP we observed presumably resulted from the supine position of our subjects as well as their lack of familiarity with this test of respiratory function, in which learning improves performance. Our measurements of VC were 85% of predicted normal before spinal, and 88% of predicted normal during spinal anesthesia. Furthermore, the potential inhibitory effect of spinal anesthesia on respiratory muscle function would tend to decrease ventilatory responsiveness, not increase it as we observed. Indeed, our measurements of occlusion pressure ( $P_{0.1}$ ) provide further support for increased ventilatory responsiveness with spinal anesthesia.  $P_{0.1}$  is a measure of central respiratory drive (20). Respiratory muscle weakness has much less effect on  $P_{0.1}$  than on  $\dot{V}_E$ ; with increasingly severe muscle weakness produced by curare,  $\dot{V}_E$  fails to increase with hypercapnia, whereas the  $P_{0.1}$  response remains intact or even increases (21). Our observation of a greater increase in  $P_{0.1}$ -55 than in  $\dot{V}_E$ -55 (32 vs 19%) is consistent with

the notion that the magnitude of the bupivacaine-induced increase in ventilatory response to hypercapnia may be underestimated by the response of  $\dot{V}_E$ .

We speculate that deafferentation of chest wall receptors by spinal anesthesia may be the cause of the increased ventilatory responsiveness in our patients. A similar mechanism has been proposed to explain the sensation of difficulty in breathing experienced by some patients during spinal anesthesia (22). To the extent that afferent input from the chest wall exerts an inhibitory effect on ventilation and sensations of breathlessness, spinal anesthesia should, therefore, result in greater increases in ventilatory responsiveness than lower spinal levels. Although no such correlation is apparent in our data, we studied only ten patients. None of our patients was short of breath during spinal anesthesia; perhaps patients who experience dyspnea with spinal anesthesia would show greater increase in  $\text{CO}_2$  responsiveness. Experimental evidence in support of an inhibitory role for chest wall receptors in control of ventilation is provided by preliminary data of Bellemore and Garzaniti (23) who noted diaphragmatic inhibition by activation of cutaneous afferents in dogs. On the other hand, chronic deafferentation of the chest wall in human quadriplegics was associated with diminished ventilatory responsiveness to hypercarbia in preliminary observations of Schwartzstein et al. (24).

In conclusion, we have shown that ventilatory responsiveness to  $\text{CO}_2$  rebreathing is increased with 0.5% bupivacaine spinal anesthesia. We speculate that the increased response may be the result of elimination of inhibitory effects of chest wall afferents.

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## Beneficial Effect of Cyclooxygenase Inhibition on Adverse Hemodynamic Responses after Protamine

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HOBBHAHN J, CONZEN PF, ZENKER B, GOETZ AE, PETER K, BRENDEL W. Beneficial effect of cyclooxygenase inhibition on adverse hemodynamic responses after protamine. *Anesth Analg* 1988;67:253-60.

*The hypothesis that adverse effects observed when heparin is antagonized by protamine are mediated by metabolites of the arachidonic acid cascade was tested during general anesthesia (enflurane, fentanyl) in 16 pigs classified into two groups. In the first group (n = 9), effects of intravenously administered protamine on systemic hemodynamics, blood/gas tensions, and arterial and mixed-venous prostanoid levels were studied. The second group (n = 7) was pretreated with indomethacin 10 mg/kg, and the same measurements were made. All pigs received heparin 150 units/kg. When protamine  $1.1 \pm 0.1$  mg/kg was administered over 3 minutes, marked hemodynamic alterations were observed in group 1: pulmonary artery pressure and pulmonary vascular resistance increased, and left ventricular end-diastolic and systemic arterial pressures decreased.*

*Arterial and mixed-venous  $PO_2$  values deteriorated in all pigs in group 1 at the end of protamine infusion. These alterations were accompanied by significantly elevated prostanoid levels in arterial and mixed-venous plasma samples: Thromboxane  $A_2$ , prostaglandin  $F_{2\alpha}$ ,  $KH_2$ -PGF $_{2\alpha}$  (a metabolite of prostaglandin  $F_{2\alpha}$ ), and prostacyclin were maximally elevated at completion of protamine and remained significantly above control values at 5 minutes but were not significantly different from control after 10 minutes. Blocking the cyclooxygenase cascade by pretreatment of the pigs with indomethacin (group 2) prevented hemodynamic and blood gas alterations. It is concluded that in pigs the detrimental side effects associated with the use of protamine to reverse heparin are mediated by metabolites of the cyclooxygenase cascade. This was evidenced in the present study by 1) elevated prostanoid levels in pigs in group 1 and 2) by the absence of side effects after protamine in the cyclooxygenase-inhibited pigs in group 2.*

**Key Words:** BLOOD, COAGULATION—protamine. HORMONES—prostaglandins.

Protamine has been widely used in the reversal of the anticoagulant effects of heparin for many years (1). The hemodynamic effects of this neutralization, including significant hypotension and a deterioration of arterial  $PO_2$ , have been described in intact animals (2-8). However, studies on cardiopulmonary bypass indicate that protamine is associated with much less hemodynamic side effects in humans (9-14). Reasons for these divergent findings and the intimate mechanisms involved in the adverse hemodynamic effects of protamine have not been elucidated, however. Histamine release has been said to play a role (12),

but histamine does not appear to be the only mediator (4,10). Another possibility is that protamine acts on activation of the complement system (10).

A previous study suggested that the cyclooxygenase pathway may be involved in reactions to protamine (7): pretreatment with acetylsalicylic acid reduced but did not completely eliminate the cardiovascular effects of protamine in heparin reversal. The authors did not, however, prove that cyclooxygenase inhibition was complete. In the present study, we reexamined the role of cyclooxygenase products of the arachidonic acid cascade during heparin-protamine interactions in intact animals. We did this by measuring cardiovascular responses and plasma prostanoid levels after neutralization of heparin by protamine with and without pretreatment with the cyclooxygenase inhibitor indomethacin to completely block endogenous prostanoid production.

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## Methods

The experiments were performed in 16 pigs weighing an average of 32 kg (range 26–38). Food was withheld for 12 hours before induction of anesthesia with IM ketamine 12 mg/kg, flunitrazepam 0.1 mg/kg, and 0.5 mg atropine. After tracheotomy, the lungs were ventilated (Servo-Ventilator 900 B, Siemens, Erlangen, West Germany) with a mixture of O<sub>2</sub> and N<sub>2</sub>O with a positive end-expiratory pressure of 3 cm H<sub>2</sub>O to prevent atelectasis. Carbon dioxide concentrations in the pigs' expired air were continuously monitored, and the tidal volume of the respirator was set to maintain end-expiratory CO<sub>2</sub> at 4.5 vol%. Anesthesia was maintained by fentanyl 0.1 mg·kg<sup>-1</sup>·hr<sup>-1</sup> and enflurane 0.6–0.8 vol%.

Monitoring of hemodynamic variables and blood sampling for biochemical and blood/gas analysis required two large-bore polyethylene catheters placed through cutdowns into the femoral vessels, the arterial catheter for measurement of mean arterial pressure (MAP) and blood sampling, and the venous line for infusion of drugs. Two Swan-Ganz catheters (5F and 7F) advanced into the pulmonary artery from the external jugular veins served for determination of the mean pulmonary artery pressure (MPAP) and cardiac output (CO) (5F) and for blood samples to measure gas tensions and prostanoid levels (7F). Cardiac output was determined in triplicate by injection of 5 ml ice-cold saline (CO-computer 9530, Mansfield Inc., Mansfield, MS). A catheter-tip manometer (Milar-Instruments, Houston, TX) was placed in the left ventricle through the right common carotid artery. This high-fidelity pressure transducer served for measurement of left ventricular end-diastolic pressure (LVEDP). Blood/gas tensions and pH in the anaerobically collected blood samples were measured using an ABL300 (Radiometer, Copenhagen, Denmark).

The pigs were randomly assigned to two experimental groups: In group 1 (*n* = 9), heparin was followed by an infusion of protamine. In group 2 (*n* = 7), 10 mg/kg indomethacin was infused IV before heparin/protamine. Baseline recordings of hemodynamic and blood/gas data were made, and blood samples for prostanoid determinations were obtained in all pigs after they had stabilized for at least 60 minutes after the surgical procedures for infusion of indomethacin (*t*<sub>0</sub>). The pigs were then given heparin 150 units/kg. Recordings were repeated after 5 (*t*<sub>1</sub>) and 15 minutes (*t*<sub>2</sub>).

Protamine (Protaminsulfat Novo) was given 2 mg/kg over 3 minutes. This amount was considered to be sufficient to antagonize circulating heparin. However, infusion was stopped immediately after

increases in pulmonary artery or decreases in systemic arterial pressures were observed. Arterial and mixed-venous blood samples were withdrawn and pressure recordings obtained immediately after the completion of the infusion (*t*<sub>3</sub>) and 5 (*t*<sub>4</sub>) and 15 minutes (*t*<sub>5</sub>) later. Cardiac output was determined after 5 (*t*<sub>4</sub>) and 15 minutes (*t*<sub>5</sub>).

Concentrations of the following prostanoids were measured in arterial and mixed venous plasma by radioimmunoassays: Thromboxane A<sub>2</sub> (TXA<sub>2</sub>), prostacyclin (PGI<sub>2</sub>), prostaglandin F<sub>2α</sub>, and its major degradation product, 13-14-dihydro-15-keto prostaglandin F<sub>2α</sub> (KH<sub>2</sub>PGF<sub>2α</sub>). Because PGI<sub>2</sub> and TXA<sub>2</sub> are chemically unstable with short half-lives in aqueous solutions, they were measured by their stable oxidation products, thromboxane B<sub>2</sub> (TXB<sub>2</sub>) and 6-keto-PGF<sub>1α</sub>, respectively. For this purpose, 3 ml blood was collected from the catheters in the pulmonary artery and the abdominal aorta into precooled plastic syringes. The syringes contained 0.1 ml indomethacin (1 mg/ml) and 0.2 ml sodium-EDTA (77 mM). The blood was immediately centrifuged at 3500 rpm at 4°C for 15 minutes. The plasma was stored at -70°C until analysis.

All prostanoids were analyzed by specific radioimmunoassays using single antibody techniques. Free and antibody-bound antigen fractions were separated by Dextran-coated charcoal. All standard curves demonstrated parallelism in buffer and in plasma. Plasma samples were run in duplicate and the mean values used for further processing of the data. Tritiated prostaglandins and prostaglandin standards were purchased from Amersham Co. and Upjohn Co., respectively. All antibodies were purchased from Pasteur-Diagnostics, Paris. The sensitivities of our assays are: 20 pg/ml for TXB<sub>2</sub>, 50 pg/ml for 6-keto-PGF<sub>1α</sub>, 10 pg/ml for PGF<sub>2α</sub> and KH<sub>2</sub>PGF<sub>2α</sub>, respectively. Cross-reactivities of the antibodies as indicated by the manufacturer were <10% for the tested metabolites.

## Statistical Analysis

Results are expressed as means ± SE. Analysis of the raw data revealed, however, that certain of the data were not normally distributed. Inner-group data following heparin or protamine were therefore analyzed by the Friedman rank analysis of variance. This was followed by Wilcoxon and Wilcox multiple comparisons to determine times at which the results were significantly different from baseline. Comparisons between groups at *t*<sub>0</sub> were performed using original data by the Wilcoxon-U test. For comparison of data after protamine was given (*t*<sub>3</sub>–*t*<sub>5</sub>), we first calculated

Table 1. Hemodynamic Data in Untreated Pigs in Group 1\*

	t <sub>0</sub>	t <sub>1</sub>	t <sub>2</sub>	t <sub>3</sub>	t <sub>4</sub>	t <sub>5</sub>
HR (sec <sup>-1</sup> )†	102 ± 5	104 ± 5	103 ± 5	139 ± 10	118 ± 6	118 ± 6
MAP (mm Hg)	85 ± 4	86 ± 4	88 ± 3	53 ± 9*	87 ± 4	86 ± 4
MPAP (mm Hg)	17 ± 1	18 ± 1	18 ± 1	35 ± 3*	27 ± 3*	19 ± 1
CO (ml·min <sup>-1</sup> ·kg <sup>-1</sup> )	152 ± 14	149 ± 12	159 ± 11	—	162 ± 14	163 ± 6
SVR (dynes·sec·cm <sup>-5</sup> )	1655 ± 140	1752 ± 152	1663 ± 74	—	1643 ± 120	1699 ± 140
PVR (dynes·sec·cm <sup>-5</sup> )	145 ± 33	183 ± 35	149 ± 18	—	393 ± 60*	222 ± 25
Pao <sub>2</sub> (mm Hg)	114 ± 4	111 ± 3	113 ± 3	98 ± 6*	102 ± 6*	105 ± 6
Pvo <sub>2</sub> (mm Hg)	44 ± 1	43 ± 1	42 ± 1	31 ± 3*	41 ± 3	44 ± 1

\*Values are given as means ± SE before (t<sub>0</sub>) and 5 (t<sub>1</sub>) and 15 (t<sub>2</sub>) minutes after heparin injection, and 2 (t<sub>3</sub>), 5 (t<sub>4</sub>), and 15 (t<sub>5</sub>) minutes after injection of protamine sulfate.

†Abbreviations: HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; Pao<sub>2</sub>, Po<sub>2</sub> in arterial blood; Pvo<sub>2</sub>, Po<sub>2</sub> in mixed venous blood.

\*P < 0.05 versus t<sub>2</sub> (baseline, immediately before infusion of protamine).

Table 2. Hemodynamic Data in the Indomethacin-Pretreated Pigs in Group 2\*

	t <sub>0</sub>	t <sub>1</sub>	t <sub>2</sub>	t <sub>3</sub>	t <sub>4</sub>	t <sub>5</sub>
HR (sec <sup>-1</sup> )†	87 ± 5	85 ± 4	80 ± 4	81 ± 4	81 ± 4	80 ± 4
MAP (mm Hg)	97 ± 3	94 ± 3	96 ± 2	92 ± 4†	93 ± 3	92 ± 4
MPAP (mm Hg)	19 ± 1	19 ± 1	19 ± 2	20 ± 2†	19 ± 2	18 ± 1
CO (ml·min <sup>-1</sup> ·kg <sup>-1</sup> )	107 ± 6	102 ± 5	100 ± 6	—	98 ± 6	98 ± 5
SVR (dynes·sec·cm <sup>-5</sup> )	2443 ± 91	2571 ± 120	2621 ± 169	—	2638 ± 212	2557 ± 175
PVR (dynes·sec·cm <sup>-5</sup> )	216 ± 54	252 ± 76	262 ± 86	—	260 ± 70†	257 ± 63
Pao <sub>2</sub> (mm Hg)	106 ± 1	105 ± 2	105 ± 3	105 ± 3†	106 ± 2†	104 ± 3
Pvo <sub>2</sub> (mm Hg)	37 ± 1	36 ± 1	36 ± 1	36 ± 1	37 ± 1	37 ± 1

\*All values are means ± SE. Determination were obtained before (t<sub>0</sub>) and 5 (t<sub>1</sub>) and 15 (t<sub>2</sub>) minutes after heparin injection, and 2 (t<sub>3</sub>), 5 (t<sub>4</sub>), and 15 (t<sub>5</sub>) minutes after infusion of protamine.

†For abbreviations see Table 1.

\*P < 0.05 versus corresponding time in group 1.

the absolute differences to the corresponding baseline values at t<sub>2</sub>. This was necessary to avoid statistical errors due to divergent baseline values. Comparisons (Wilcoxon-U test) were then made using these differences. P < 0.05 was considered statistically significant.

## Results

Indomethacin blocked cyclooxygenase completely. This was evidenced by plasma prostanoid levels not different from zero. Because of inhibition of the cyclooxygenase cascade, systemic vascular resistance (SVR) was higher and CO and mixed venous Po<sub>2</sub> were significantly lower in group 2 than in group 1.

Injection of heparin into the right atrium was not followed by changes in hemodynamics, blood/gas tensions, or prostanoid levels in either group (Tables 1 and 2).

### Group 1, Unblocked Animals

Infusion of protamine increased MPAP and decreased LVEDP and MAP (Table 1, Figs. 1 and 2).

This was concomittant with decreases in arterial and mixed-venous Po<sub>2</sub> (Table 1), as well as a decrease of end-expiratory CO<sub>2</sub> (Fig. 1). Because protamine infusion was stopped as soon as hemodynamic effects were observed, no pig received the full dose required to completely antagonize heparin. Average protamine infusion amounted to 1.1 ± 0.1 mg/kg. Maximal hemodynamic and blood/gas changes were observed 2-4 minutes after start of the protamine infusion.

Also at t<sub>3</sub>, the most pronounced changes of plasma prostanoid levels were observed (Fig. 3). Arterial levels of TXB<sub>2</sub>, PGF<sub>2α</sub>, KH<sub>2</sub>PGF<sub>2α</sub>, and PGI<sub>2</sub> increased to 460, 220, 690, and 150% of their initial values. Venous and arterial prostanoid levels were not significantly different from each other. All changes were most pronounced at the end of protamine infusion (t<sub>3</sub>). At 5 minutes (t<sub>4</sub>), MPAP, the transpulmonary pressure gradient, and pulmonary vascular resistance (PVR) were still significantly above t<sub>2</sub> levels (Table 1, Fig. 2), but after 10 minutes (t<sub>5</sub>), they had returned toward control (t<sub>2</sub>). We could not obtain reliable cardiac output determinations (triplicate injections of cold saline) at completion of protamine because of

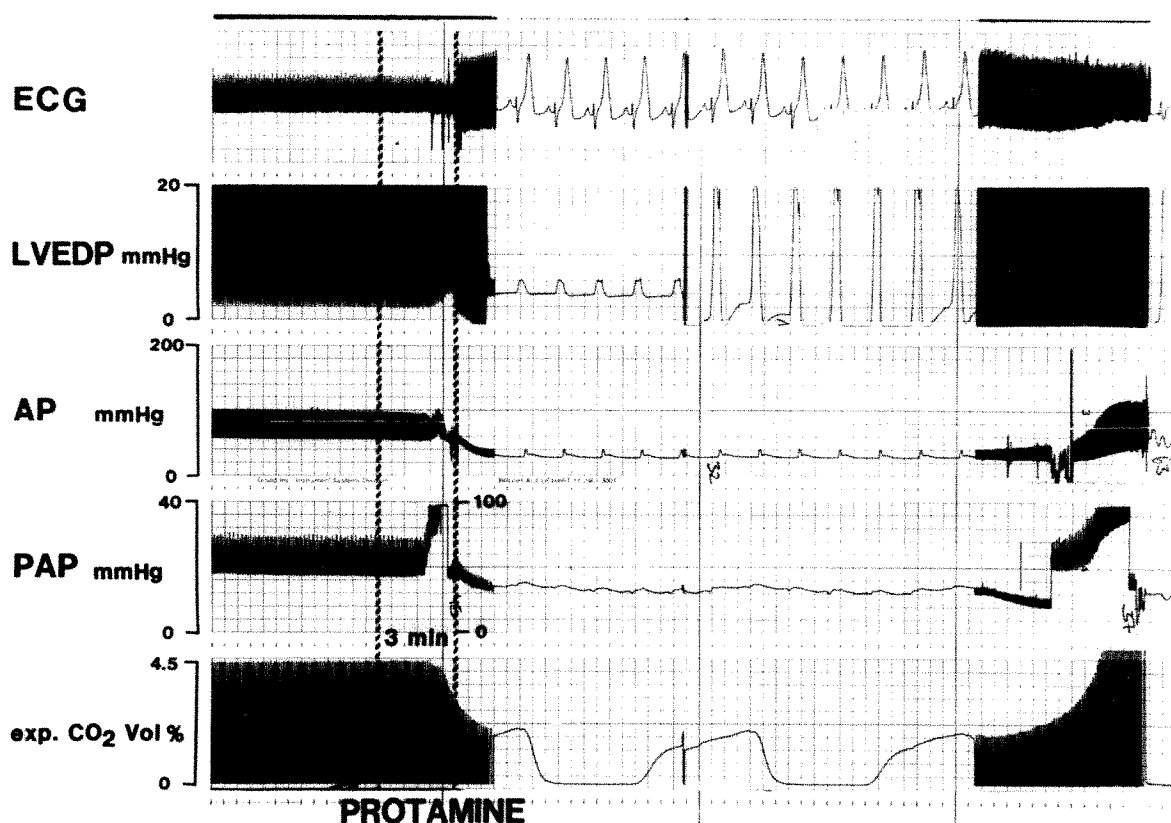


Figure 1. Acute pulmonary hypertension and decreased left ventricular filling in a representative animal of group 1. Protamine denotes the period of protamine infusion (3 minutes). Note that the precipitous increase in pulmonary artery pressure (PAP, mm Hg) required reduction of the pressure amplification from 40 to 100 mm Hg full scale. Left ventricular end-diastolic pressure (LVEDP, mm Hg) and systemic arterial pressure (AP, mm Hg) decreased subsequent to the increase in PAP. End-expiratory CO<sub>2</sub> (vol%) decreased to about 50% of its initial value. Note the change in time scale about 1 minute after end of protamine infusion.

hemodynamic instability. Single measurements indicated, however, that CO was decreased about 50–60% at that time.

#### *Indomethacin-Treated Animals (Group 2)*

The cyclooxygenase-blocked pigs had no changes in hemodynamics, blood/gas tensions, or prostanoid levels even though the full amount of protamine (2 mg/kg) was infused. Comparison with pigs in group 1 revealed significant differences in MAP, MPAP, arterial and mixed-venous Po<sub>2</sub> (Table 2), and the transpulmonary pressure gradient (Fig. 3) at t<sub>3</sub>. MPAP, PVR, and the transpulmonary pressure gradient remained significantly different from the unblocked pigs at 5 minutes after protamine (t<sub>4</sub>).

#### Discussion

The results of this study indicate that, in our porcine model of heparin-protamine interactions, endoge-

nously liberated prostanoids not only contributed to, but mediated, the adverse protamine effects. This was demonstrated by significantly increased plasma prostanoid levels immediately after heparin reversal with protamine. Maximal prostanoid concentrations coincided with maximal hemodynamic changes. Findings in our second group of pigs demonstrated that cyclooxygenase activity was necessary for the hemodynamic and blood/gas effects of protamine, which were completely prevented by pretreatment with indomethacin.

We know from a large number of our own studies and from others (15–17) that infusion of 10 mg/kg indomethacin blocks cyclooxygenase completely. We also know that blocking cyclooxygenase in pigs increases systemic pressures and vascular resistances. This effect of prostaglandin inhibition, also noted by others (18–20), is not species specific and may be due to the fact that continuous vascular prostanoid production contributes to a low vascular tone (21). To avoid statistical interference with divergent control values, intergroup comparisons after protamine



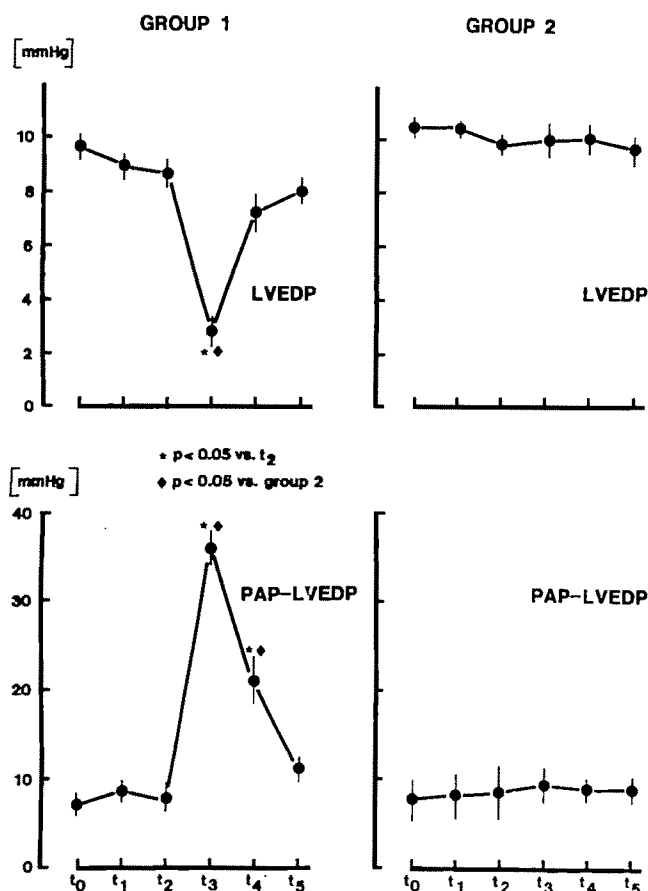


Figure 2. Left ventricular end-diastolic pressures (LVEDP) and the transpulmonary pressure gradients (MPAP-LVEDP) in all pigs at baseline ( $t_0$ ), and 5 ( $t_1$ ) and 15 ( $t_2$ ) minutes after infusion of 150 units/kg heparin. Protamine was infused immediately after  $t_2$ . Measurements were then repeated 2 ( $t_3$ ), 5 ( $t_4$ ), and 15 ( $t_5$ ) minutes after protamine.

were, therefore, based on absolute differences ( $t_2$ - $t_3$ , etc.).

Time-course analysis revealed that the pivotal step for the hemodynamic alterations after protamine is pulmonary vasoconstriction. This is evidenced by increases of the transpulmonary pressure gradient and pulmonary vascular resistance (Table 1, Fig. 2). Pulmonary vasoconstriction as a primary cause of acute cardiovascular deterioration in humans or in animals when heparin is reversed by protamine has also been reported by others (5,22-25). As a consequence, left ventricular filling as reflected by left ventricular end-diastolic pressure is significantly reduced (Fig. 2). Thus, reduction in stroke volume is responsible for the decreases in arterial pressure and cardiac output. The decrease in arterial pressure may furthermore be aggravated by significantly elevated prostacyclin levels (Fig. 3).

Our results indicate that pulmonary vasoconstriction is caused by liberation of  $TXA_2$  and  $PGF_{2\alpha}$ .  $TXA_2$

has long been recognized to be a potent pulmonary vasoconstrictor, mainly released from platelets (26).  $PGF_{2\alpha}$  appears to be a less potent vasoconstrictor (27). The mediator role of these prostanoids for the increased pulmonary vascular resistance is demonstrated in the indomethacin-pretreated animals, where radioimmunoassays of the plasma samples did not reveal detectable concentrations. The absence of hemodynamic side effects also suggests that the amount of indomethacin infused was sufficient to block cyclooxygenase complete.

Whereas arterial and mixed-venous levels of  $TXA_2$  and  $PGI_2$  were almost identical and did not allow a conclusion to be drawn about their sites of origin, analysis of  $PGF_{2\alpha}$  indicates an intrapulmonary activation. Normally more than 90% of IV infused  $PGF_{2\alpha}$  is metabolized during the first passage through the lungs (27).  $PGF_{2\alpha}$  levels in mixed-venous plasma samples of the pigs of group 1 were generally lower than in arterial blood, indicating that the source of production is located within the lungs. Also, the mixed-venous  $PGF_{2\alpha}$  changes did not reach the level of statistical significance in the Friedman analysis. It appears that, at least when heparin is antagonized by protamine given intravenously, arachidonic cascade activation occurs in the lungs as the first vascular filter.

Radegran et al. (6) surmised in 1971 that protamine exerts its hemodynamic and respiratory side effects in the lungs via release of a smooth muscle-stimulating substance from aggregated platelets. The relevance of cyclooxygenase in heparin/protamine interactions was also noted in a subsequent study. Radegran and McAslan (7) reported that acetyl-salicylic acid injected before protamine significantly inhibited protamine-induced increases in MPAP and PVR in dogs. However, hemodynamic alterations were not completely prevented. Unfortunately these authors did not provide information about completeness of cyclooxygenase blockade in their study animals. On the basis of our results it appears possible that the still present although reduced hemodynamic side effects of protamine in their study were indeed due to residual cyclooxygenase activity.

McIntyre et al. (28) reported elevation of plasma  $TXB_2$  and 6-keto- $PGF_{1\alpha}$  levels in a 60-year-old man undergoing cardiopulmonary bypass after 100 mg protamine injected over 2 minutes. This was accompanied by a marked increase in pulmonary artery pressure and a decrease in arterial pressure. Recently, Morel et al. (10) investigated 48 adult patients after cardiopulmonary bypass in a prospective study. Two patients developed acute pulmonary hypertension with plasma thromboxane  $B_2$  levels of 7.5 and 16.2 ng/ml 1 minute after protamine injection. These

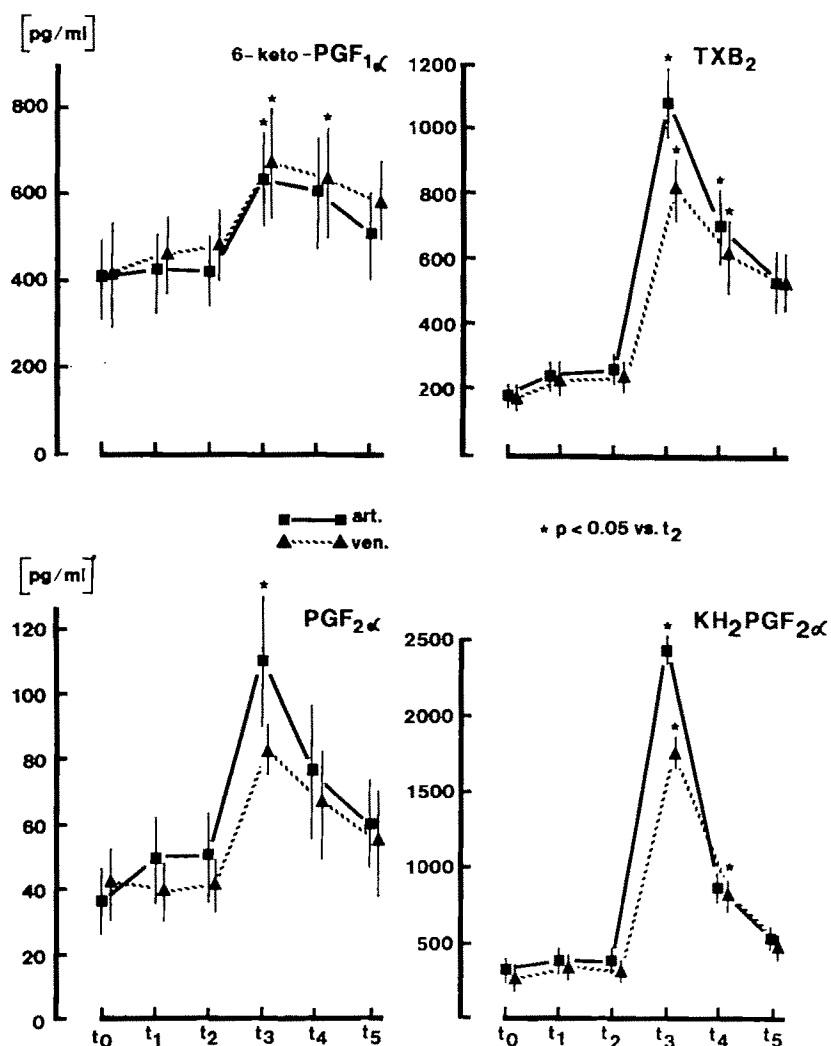


Figure 3. Arterial and mixed-venous plasma prostanoide concentrations in the cyclooxygenase unblocked animals of group 1. Abbreviations: TXB<sub>2</sub>, metabolite of thromboxane A<sub>2</sub>; PGF<sub>2α</sub>, prostaglandin F<sub>2α</sub>; KH<sub>2</sub>PGF<sub>2α</sub>, metabolite of PGF<sub>2α</sub>; 6-keto-PGF<sub>1α</sub>, metabolite of prostacyclin. See Figure 2 for abbreviations.

observations in humans and our findings in pigs strengthen the necessity of considering preoperative intake of cyclooxygenase inhibitors when protamine effects are studied in humans. In addition to their analgesic effects, cyclooxygenase inhibitors are effective in patients with vascular diseases, because they have been shown to exert beneficial effects on thrombocyte aggregation (29). It should be kept in mind that thrombocytes normally circulate for about 10 days and that they do not have the enzymatic capacity to resynthesize previously blocked cyclooxygenase (30). This may be related to the inconsistent findings on the cardiovascular effects of protamine in human studies (9-14).

Another important aspect is the rate of infusion of protamine. As early as 1949, Jaques (2) noted in dogs that infusion of protamine 5-10 mg/kg over 4 minutes was benign, but the same dose over 15 seconds decreased systemic blood pressure to a value near 30 mm Hg. Our experimental protocol was designed to antagonize all heparin over 3 minutes. Similar rates of

infusion are used clinically (14,28) and experimentally (6,8) by others. We stopped infusion as soon as pulmonary artery pressure started to increase. This led to a mean infused protamine dose of 1.1 mg/kg and to approximately 70% reversal of heparin (31). Thus, unusually high protamine levels or rapid injection were not produced in the present study.

We also excluded the possibility that protamine by itself induced hemodynamic effects. In five pilot experiments, protamine alone, infused in a dose of 2 mg/kg, failed to induce any changes. This was also reported by Stefaniszyn et al. (23) and Rogers et al. (5), who found no hemodynamic alterations when protamine alone was infused in comparable concentrations.

Why, then, was the decrease in arterial pressure not compensated by an increased peripheral resistance? We could not obtain reliable measurements of cardiac output (mean of triplicate injections with a variability of <5%) during the first 2 minutes after protamine and did not calculate systemic vascular resistance. Although SVR has been reported to be

slightly elevated immediately after protamine in pigs, this increase was not sufficient to maintain arterial pressure (5). We assume that this lack of compensation is at least in part due to the release of the vasodilating  $\text{PGI}_2$ . Another possibility is that the vascular reflex mechanisms were overridden by the anesthetic regimen. In fact, especially in the human investigations, systemic vascular resistance has often been reported to be decreased rather than increased (9,11-13). This discrepancy again raises the question of pretreatment of the patients. Whereas circulating platelets can be irreversibly blocked by cyclooxygenase inhibitors (30), endothelial cells will regain the capacity for production of prostanoids and hence of  $\text{PGI}_2$  after a relatively short period (32,33). Prostacyclin production could therefore explain why systemic vascular resistance even decreases in some investigations. However, thrombocyte function in animals may not be comparable to that in humans, particularly after extracorporeal circulation. Cardiopulmonary bypass in general decreases thrombocyte counts and, furthermore, may be associated with a reduced thromboxane generating capacity of the remaining platelets. Thus, if cardiopulmonary bypass by itself influences the  $\text{TXA}_2$ -generating capacity of the platelets, the variation in systemic and pulmonary hemodynamic responses to protamine might be explained (10,12,22,34,35).

In conclusion, the adverse hemodynamic effects that we observed in pigs associated with protamine reversal of heparin were mediated by intrapulmonary activation of the arachidonic acid cascade. The increased pulmonary vascular resistance in this study is best explained by liberation of the vasoconstricting prostanoids  $\text{TXA}_2$  and  $\text{PGF}_{2\alpha}$ .  $\text{PGI}_2$  may partially be responsible for the low systemic vascular resistance despite a decreased systemic arterial pressure. Protamine-induced hemodynamic side effects were, however, prevented by pretreating the pigs with the cyclooxygenase inhibitor, indomethacin. Although we did not determine histamine or complement activation in our pigs, the results indicate that the hemodynamic influences of these systems are negligible as compared to the role of the cyclooxygenase cascade. The mechanisms responsible for arachidonic acid cascade activation after reversal of heparin by protamine and the applicability of these results to humans remain to be elucidated.

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## Postoperative Effects of Intrathecal Morphine in Coronary Artery Bypass Surgery

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VANSTRUM GS, BJORNSON KM, ILKO R. Postoperative effects of intrathecal morphine in coronary artery bypass surgery. *Anesth Analg* 1988;67:261-7.

*To determine whether intrathecal morphine is effective in decreasing analgesic and antihypertensive drug requirements after coronary artery bypass (CAB) surgery, a prospective, randomized, double-blind study was designed. Approximately 30 minutes before induction of anesthesia with IV sufentanil and diazepam, and 2 hours before heparinization, one group of patients (n = 16) were given morphine 0.5 mg, while the control group (n = 14) were given placebo intrathecal injections through 22- or 25-gauge lumbar puncture needles. Intraoperatively, there were no differences in the numbers of patients requiring vasodilator drugs or volatile agent titration. During the postoperative period, the treated group required significantly less ( $P <$*

*0.05) IV morphine compared with the placebo group, during the first 24 hours ( $1.8 \pm 0.7$  vs  $5.4 \pm 1.5$  mg) and 30 hours ( $2.4 \pm 0.8$  vs  $8.3 \pm 1.9$  mg). The treated group also required significantly less ( $P < 0.05$ ) sodium nitroprusside in the first 24 hours ( $58.1 \pm 29.0$  vs  $89.1 \pm 18.4$  mg). There were no differences in pain scores, and the only complications (itching, nausea and vomiting) were infrequent. It is concluded that an intrathecal dose of 0.5 mg of morphine is efficacious in reducing analgesic and antihypertensive drug requirements after CAB surgery. Whether these results are clinically important enough to warrant the theoretical risks of postheparinization lumbar hematoma is a topic for further investigation.*

**Key Words:** ANESTHESIA—cardiovascular. ANALGESICS—morphine. PAIN—postoperative. ANESTHETIC TECHNIQUES, SPINAL—morphine.

A decade after the discovery of endorphins (1) and their receptors (2) in the mid-1970s, the clinical use of opiates in the intrathecal and epidural spaces continues to be extended to new applications (3). Initial clinical work in cancer patients (4) with pain has been followed by the widespread use of spinal opiates for postoperative pain management (5-8). Although spinal opiates are used at a few cardiac centers, there are only two published works on the use of subarachnoid opiates in cardiac surgery. Matthews and Abrams (9) presented a brief, noncontrolled report of their use of intrathecal morphine in 40 cardiac surgery patients. They believed the technique offered potential advantages to their patients and deserved further study. Vincenty et al. (10) presented a study that compared the use of a large dose of intrathecal morphine (10 mg) in ten patients anesthetized with 20-50  $\mu\text{g/kg}$  fentanyl with a second group of ten patients anesthe-

tized with 100-150  $\mu\text{g/kg}$  fentanyl alone. Although the study was not performed in a double-blind manner, the investigators did demonstrate significantly less need for both intraoperative nitroglycerin and postoperative IV morphine in patients given intrathecal morphine. The possible merit of intrathecal morphine in cardiac bypass surgery suggested by these two reports deserves further examination. Consequently, we designed a prospective, randomized, double-blind study to decide if benefits from the procedure can be objectively demonstrated and, if so, to determine, if possible, whether such benefits outweigh the risks of lumbar puncture before CAB surgery.

### Methods

After approval by our Institutional Review Committee, written informed consent was obtained from 30 ASA physical class IV patients requiring elective coronary artery bypass surgery. Any patients with a previous sternotomy or preoperative insertion of an intraaortic balloon pump, and any patients requiring

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reexploration within 48 hours of the initial operation were excluded from the study.

Preoperative medication with  $\beta$ -blockers, calcium channel blockers, and nitrates was continued until 1 hour before surgery. Preanesthetic medication 30 minutes before arrival in the operating room included intramuscular scopolamine 0.005 mg/kg, intramuscular morphine sulfate 0.16 mg/kg, and diazepam 0.14 mg/kg by mouth; oxygen at 4 L/min was also given by nasal cannula. Automatic blood pressure and ECG monitors were applied on arrival in the operating room, and a large-bore IV cannula was inserted in a peripheral vein. The patients were then placed in the left lateral decubitus position. After cleaning the lumbar spine with Povidone-iodine solution and the administration of a 1% lidocaine local anesthetic, a lumbar puncture was performed with a 22- or 25-gauge needle. If more than 10 minutes were required to penetrate the subarachnoid space, the attempt was abandoned and that patient dropped from the study. Patients were given either 1 ml of saline or 1 ml of 0.05% preservative-free morphine (Duramorph, AH Robins) intrathecally in a double-blinded manner in accordance with a randomly coded schedule provided to the pharmacy by our statistician.

After lumbar puncture, the patients were returned to the supine position, and radial and pulmonary artery catheters were inserted. One hundred percent oxygen was then given and anesthesia induced with sufentanil 7  $\mu$ g/kg in 50- $\mu$ g increments, diazepam 0.14 mg/kg, pancuronium 0.07 mg/kg, and metocurine 0.14 mg/kg. Isoflurane 0.25 to 1.0%, was used to prevent hypertension and tachycardia. No further narcotic was administered for maintenance of anesthesia.

In the surgical intensive care unit (ICU), morphine sulphate was administered intravenously in 2-mg increments every 30 minutes as needed for pain. Pain scores, determined by the linear analogue pain score (11), were recorded at 12, 18, 24, and 30 hours after admission to the ICU. Nurses attempted to keep the pain score at less than 4 in all patients (a score of 1 represented no pain, 10 represented the worst pain imaginable; the scale was 25 cm long). Intravenous sodium nitroprusside, nitroglycerin and hydralazine were given as needed to keep blood pressure < 140/90 mm Hg, pulmonary artery occlusion pressure < 18 mm Hg, and systemic vascular resistance < 1200 dynes $\cdot$ sec $\cdot$ cm $^{-5}$ . Cumulative doses of morphine and antihypertensive drugs, times of extubation, and blood gas tensions after extubation were recorded. Mechanical ventilation was supported until the morning after surgery, at which time patients were extubated.

Table 1. Patient Characteristics\*

	Group I Morphine	Group II Placebo
n	16	14
Sex	1F:15M	3F:11M
Height (cm)	176 $\pm$ 1.3	174 $\pm$ 2.7
Weight (kg)	83.8 $\pm$ 3.3	74.0 $\pm$ 6.4
Age (yr)	63.7 $\pm$ 2.9	66.8 $\pm$ 3.1
No. of preoperative antihypertensive meds	2.1 $\pm$ 0.9	1.4 $\pm$ 0.7

\* $P > 0.15$  for all data. Data are presented as mean  $\pm$  SEM.

Data were analyzed using the Mann-Whitney *U* test and are presented as mean  $\pm$  SEM. In addition, we employed the average rank test as a measure of combined antihypertensive drug use (see below), and the  $\chi^2$  test for examining intraoperative drug use and the association of patients who required zero intravenous morphine and/or nitroprusside. Statistical methods were established before initiation of the study, and  $P < 0.05$  was considered statistically significant.

(Average rank and the Mann-Whitney *U* test are nonparametric tests used in statistics when a large number of zero values are present, when analyzing samples that deviate strongly from a normal distribution, and when dissimilar values of a common category are to be compared (12). In this study, for example, both groups had patients who did not require one or several of three different antihypertensive drugs. Thus a numerical order rank was assigned for each dose of a given drug, with each zero value receiving an averaged value. For example, if three patients received 0, 0, and 20 mg of sodium nitroprusside, respectively, their rank would be 1.5, 1.5, and 3.0. Averages for all three ranked drugs were assigned to each patient, and these averages were compared for the two groups by the Mann-Whitney *U* test.)

## Results

Sixteen patients received morphine 0.5 mg intrathecally (group I) and 14 received saline (group II). There were no significant differences in sex, height, weight, age, or the number of preoperative chronic antihypertensive drugs (Table 1). The shortest time between lumbar puncture and heparinization was 60 minutes, and the average time to heparinization was 1 hour 57 minutes. Both groups received similar anesthetics intraoperatively, and there were no significant differences in the number of patients who required isoflurane titration or intraoperative vasodilators (Table



Table 2. Intraoperative Isoflurane and Vasodilator Requirements\*

	Group I Morphine	Group II Placebo
Patients receiving isoflurane		
Prebypass	13 (81%)	10 (71%)
Bypass	0	0
Postbypass	0	0
Patients receiving vasodilators (nitroglycerin, nitroprusside, or hydralazine)		
Prebypass	5 (31%)	3 (21%)
Bypass	3 (13%)	2 (14%)
Postbypass	3 (19%)	4 (29%)

\* $P > 0.10$  for all data.

Table 3. Respiratory Data\*

	Group I Morphine	Group II Placebo
<i>n</i>	16	14
Time to extubation (hr)†	19 ± 1.1	22.1 ± 1.5
Arterial blood gas tensions after extubation		
pH	7.43 ± 0.01	7.43 ± 0.01
Po <sub>2</sub> (mm Hg)	102 ± 7.8	88 ± 6.0
Pco <sub>2</sub> (mm Hg)	41 ± 1.4	40 ± 0.8

\* $P > 0.10$  for all data. Data are presented as mean ± SEM.

†Data represent interval beginning with intrathecal injection.

Table 4. Pain Scores\*

	Group I Morphine	Group II Placebo
12 hrst†	2.0 ± 0.5	1.6 ± 0.4
18 hrst†	1.7 ± 0.6	3.1 ± 1.0
24 hrst†	1.7 ± 0.2	3.1 ± 0.8
30 hrst‡	2.1 ± 0.4	4.2 ± 0.8

\*Pain scores were collected at 6-hour intervals after arrival in ICU. No data were collected during the first 6 hours because patients were still asleep. Each value represents a point on a 25-cm linear analogue scale; 1 = no pain, 10 = most severe pain imaginable. Data are presented as mean ± SEM.

† $P > 0.10$ .‡ $P = 0.06$ .

2). Postoperatively, there were no significant differences in time to extubation and arterial blood gas tensions after extubation (Table 3), or in length of hospital stay.

Although the pain scores between groups were not significantly different at any time interval tested (Table 4), the total amount of IV morphine required by group II was significantly greater than that required by group I both 24 ( $5.4 \pm 1.5$  vs  $1.8 \pm 0.7$  mg) and 30 hours ( $8.3 \pm 1.9$  vs  $2.4 \pm 0.8$  mg; Fig. 1) after intrathecal injection. Also, after 24 hours in the ICU, patients in group II had required significantly more

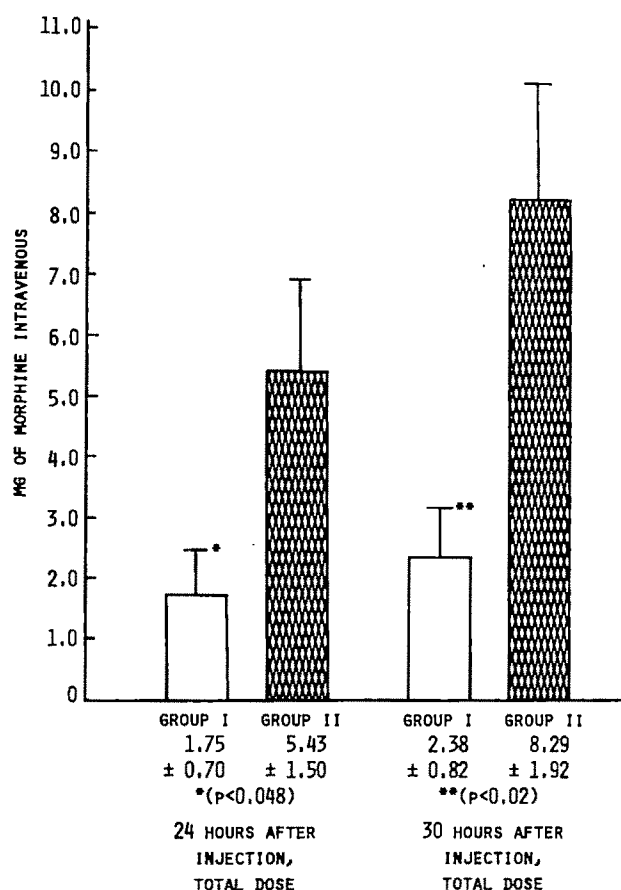


Figure 1. Postoperative supplemental IV morphine requirements. Data were recorded 24 and 30 hours after intrathecal injection. Group I received intrathecal morphine 0.5 mg; group II received intrathecal saline.

nitroprusside than those in group I ( $89.1 \pm 18.4$  vs  $58.1 \pm 29.0$  mg; Fig. 2). Although  $P$  values were not significantly different for the frequency of administration of nitroglycerin and hydralazine, as compared individually by the Mann-Whitney  $U$  test, there was a statistically increased need for antihypertensive drugs by patients in group II for all three antihypertensive drugs compared as a group by the average rank test.

Those patients were identified who were given neither morphine nor sodium nitroprusside during the first 24 hours after intrathecal injection of either morphine or placebo (Table 5). Significantly more patients in the study group did not require any morphine (63 vs 21%) or nitroprusside (50 vs 14%) postoperatively. Five patients (31%) in group I did not require either drug, and there were no such patients in group II.

Side effects were minimal in both groups: two patients in the saline group required treatment for nausea and vomiting, and one patient in the morphine group had mild pruritis that did not require

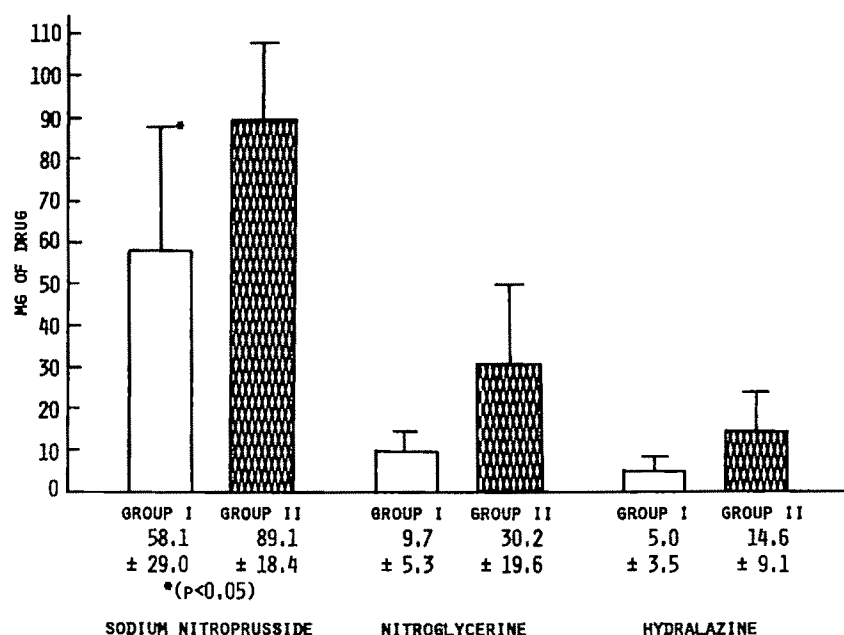


Figure 2. Postoperative antihypertensive drug requirements. Data are based on use of antihypertensive medications during the first 24 postoperative hours. Group I received intrathecal morphine 0.5 mg; group II received intrathecal saline.

Table 5. Postoperative Morphine and Nitroprusside Requirements\*

	Group I Morphine	Group II Placebo
n (Total patients)	16 (100%)	14 (100%)
Patients receiving no IV morphine†	10 (63%)	3 (21%)
Patients receiving no nitroprusside‡	8 (50%)	2 (14%)
Patients receiving neither IV morphine nor nitroprusside‡	5 (31%)	0 (0%)

\*All data represent the first 24 hours postintrathecal injection.

†P < 0.05.

‡P = 0.06.

treatment. There was no late respiratory depression and no naloxone was required. No spinal headaches occurred, and no local bleeding problems related to heparinization after lumbar puncture were noted.

## Discussion

The ideal anesthetic technique for CAB surgery should provide, in addition to intraoperative cardiovascular stability, a stable and pain-free recovery. High dose IV narcotics, whether given by the front-end loading method or by the continuous infusion method, certainly have brought current practice closer to this ideal. We reasoned that the cerebral spinal fluid (CSF) levels of morphine after intrathecal administration, which are orders of magnitude

higher than the CSF levels achieved with parenteral administration (13,14), might produce salutary effects on recovery from CAB surgery. Our study, although based on only 30 patients, demonstrated a significant reduction in analgesic and antihypertensive drug use in the ICU in those patients receiving intrathecal morphine. The price paid was a lumbar puncture before induction of anesthesia.

In designing our study, we decided to focus on the postoperative period. Our impression before the study was that there was little apparent intraoperative hemodynamic difference between patients receiving 0.5 mg intrathecal morphine and those receiving a standard narcotic anesthetic. Chester et al. (15) support this impression with a recent study, in which they were unable to demonstrate hemodynamic differences intraoperatively between patients undergoing major abdominal surgery who received 1.0 mg of intrathecal morphine and controls. In studying pharmacokinetic aspects of intrathecal morphine, Nordberg et al. (16) have shown that onset of thoracic analgesia is delayed with lumbar injection. Although the Vincenty study (10) did show decreased use of intraoperative nitroglycerin in their intrathecal morphine patients, their initial dose was 10 mg. We believed that this large dose, which most probably achieved high thoracic CSF levels early enough to be a major intraoperative factor, might predispose to respiratory depression 24 hours after injection, when our patients would be extubated. Consequently we limited our study to the smaller dose and concentrated on the examination of post-operative

analgesia and hemodynamics. We did, however, look at the numbers of patients who required intraoperative isoflurane titration or vasodilator therapy and, as expected, were unable to demonstrate significant differences (see Table 2).

The intrathecal injection of narcotics in patients about to be heparinized might be questioned. Owens et al. (17) described a patient who was heparinized 2 hours 15 minutes after a technically difficult diagnostic lumbar puncture. Sixteen hours later the patient became paraplegic. Despite timely surgical exploration and drainage of a spinal hematoma, he remained paralyzed. In a literature review, Owens et al. (17) found 33 cases of spinal hematoma reported since 1911, with 26 cases, or 79%, involving patients with evidence of hemostatic abnormality from anticoagulants, thrombocytopenia, coagulopathy, or antiplatelet therapy.

Although aware of the theoretical possibility of a spinal or epidural hematoma occurring with our protocol, we were satisfied with its safety based on the work of Rao and El-Etr (18) and Matthews and Abrams (9). The former investigators demonstrated that careful technique and willingness to postpone surgery after a difficult or bloody tap resulted in no cases of subarachnoid hematoma in 847 patients who had continuous spinal anesthesia initiated before being heparinized for vascular surgery. A 17-gauge Tuohy needle was used to place the catheter. Although the size of the spinal needle was not reported by Owens et al. (17) it may be assumed that an 18- or 20-gauge needle was used, because a diagnostic lumbar puncture includes measuring opening pressure, and this requires a larger needle. The use of 25- or 26-gauge spinal needles is relatively recent. One might speculate that the already rare complications reviewed by Owens et al. (17) might be further reduced or even eliminated by the use of small-gauge needles in combination with the cautious technique demonstrated by Rao and El-Etr (18). We now, however, avoid the use of 22-gauge spinal needles (previously used in elderly patients with osteoarthritis) and rely on the 25- or 26-gauge needles. Between 1984 and 1987, approximately 1000 of our patients undergoing cardiac surgery have received spinal narcotics without any associated neurologic complications.

Because of the possibility of a spinal hematoma, the recommendations made by Owens et al. (17) deserve attention, especially regarding their admonishment to monitor closely neurologic status postoperatively. This is a theoretical objection to our technique, because most CAB patients are unconscious for several hours after operation, precluding an accu-

rate initial postoperative neurologic exam. Unlike most of the patients in their review, however, our patients all had their heparin reversed intraoperatively with protamine.

Were the results we obtained worth the theoretical risk of lumbar puncture? One might certainly question the clinical importance of the decreased postoperative morphine requirements that we demonstrated. Nevertheless, it is noteworthy that any significant difference at all in postoperative narcotic requirements was found in our patients receiving high dose sufentanil anesthesia, and this attests to the potency of intrathecal morphine. We suspect that this decreased analgesic requirement, which alone might not be enough of a valid reason for giving the intrathecal morphine, may be associated with an improved neuropsychiatric postoperative course. Cohen and Woods (19) studied such phenomena in postcesarean patients treated with epidural morphine by examining ambulation and mother-infant bonding. Future research that quantifies this combination of alertness and analgesia by examining coordinative and reactive skills (20) may be indicated in cardiac surgery patients given intrathecal morphine. Certainly neuropsychologic dysfunction after cardiopulmonary bypass is not a negligible problem (21).

The second benefit shown in our trial was a significant decrease in postoperative administration of vasodilators. The 35% reduction in use of sodium nitroprusside in patients given intrathecal morphine suggests that they were more hemodynamically stable than were patients not given intrathecal morphine, perhaps because of lower postoperative plasma catecholamine levels. The across-the-board reductions in antihypertensive medications shown by the average rank test corroborates this trend. Fewer infusions of vasoactive drugs decrease the chance for medication error and reflect a generally more benign course.

Further evidence of the efficacy of intrathecal morphine in the CAB patient was reflected by the increased number of patients during the first 24 hours after injection who required either no IV postoperative opiates or no sodium nitroprusside (Table 5). In addition, 31% of the 16 study patients were given neither drug during the first day, compared with none of the 14 placebo patients.

Whether or not these benefits are worth the minimal chance of such a devastating, if extremely rare, complication as a spinal hematoma is not clear. Perhaps further research can answer this question, both by confirming and elaborating on the benefits we have demonstrated, and by defining the risks of



the technique in the cardiac surgery patient population.

Several points regarding drug dosage deserve comment. A recent study examining intrathecal opiates for post-thoracotomy pain used 10  $\mu\text{g/kg}$  intrathecal morphine (or 0.7 mg for a 70-kg patient) (8). This dose is slightly larger than our fixed 0.5-mg dose, which seems appropriate given that the amount of chest pain experienced by patients after a thoracotomy is greater than that after a median sternotomy (22).

An additional point involving IV morphine dosage is that even though patients in our control group needed significantly more IV morphine postoperatively than did our patients given intrathecal morphine, the cumulative IV morphine needed by the control group ( $5.4 \pm 1.5$  mg) was relatively small for 24 hours. The reasons for this are probably threefold. First, our patients received a moderate to large dose of sufentanil (7  $\mu\text{g/kg}$ ) for anesthesia and probably had analgesic blood levels persisting into the ICU period. Second, nurses were instructed to administer morphine only for complaints of pain, and not to use it for its sedative properties. Finally, the 24- and 30-hour totals for IV morphine were summated beginning with time of intrathecal injection, and thus represent only about 18 and 24 hours of ICU time, respectively, as the initial 6 hours were spent in the operating room.

Time to extubation and arterial blood gas tensions after anesthesia were not significantly affected by the use of intrathecal morphine. A feared complication of intrathecal narcotics is respiratory depression or even arrest (23,24). For this patient population, intubated and in the ICU, such events, even if they had occurred, could be dealt with safely and rapidly. Similarly, urinary retention, also a well known adverse effect of epidural and intrathecal narcotics (25) was not a problem because all patients underwent perioperative urinary catheterization. Of the remaining potential side effects, pruritis, nausea and vomiting, and spinal headache were not a problem in our patients.

In summary, the use of 0.5 mg of intrathecal morphine, administered before heparinization, provided potential benefits to our cardiac surgical patients in terms of both postoperative pain control and hemodynamic stability. Further study is needed to determine the optimal dose of intrathecal opiate that will optimize analgesic and hemodynamic stability while avoiding side effects that may be associated with intrathecal narcotics. Although our patients had no serious complications, the safety of lumbar punc-

ture in patients about to be heparinized will require further study.

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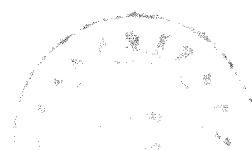
We extend special thanks to Charles Berry, PhD, C. Craig Moldenhauer, MD, Marsha Mettler, RPh, and to the Mercy ICU nursing staff and the Mercy cardiothoracic surgeons. Without their help the above study would have been impossible. A. H. Robins supplied the preservative-free morphine.

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## Pharmacokinetics of Sufentanil in Adolescent Patients with Chronic Renal Failure

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DAVIS PJ, STILLER RL, COOK DR, BRANDOM BW, DAVIN-ROBINSON KA. Pharmacokinetics of sufentanil in adolescent patients with chronic renal failure. *Anesth Analg* 1988;67:268-71.

*The role of the kidney in sufentanil elimination or metabolism has not been defined. The effects of chronic renal failure (CRF) on the pharmacokinetic profile of sufentanil were evaluated in six adolescent patients undergoing renal transplantation, and these findings were compared with data from age-matched control patients with normal renal function who were undergoing other surgical procedures. Pa-*

*tients with CRF weighed significantly less than did the control patients ( $28.7 \pm 5.7$  vs  $44.7 \pm 12.9$  kg [mean  $\pm$  SD]). Although there was no statistical difference in the rate of clearance or apparent volume of distribution and half-life between the two groups, clearance and half-life were more variable among patients with CRF. In these patients, therefore, sufentanil dose must be carefully administered based on responses elicited in individual patients.*

Key Words: ANALGESICS—sufentanil.  
PHARMACOKINETICS—sufentanil.  
KIDNEY, RENAL FAILURE—sufentanil.

Sufentanil, a potent synthetic opioid congener of fentanyl, is approximately five to ten times more potent than is fentanyl and has a high margin of safety (1,2). Sufentanil is highly lipophilic and highly protein-bound. It distributes rapidly and extensively to all tissues. Although the pharmacokinetics of sufentanil have been studied in adults (3), data regarding the pharmacokinetics of sufentanil in children are limited (4,5). Chronic renal failure (CRF) is known to severely decrease a child's growth (6-11). Because of the physiologic and anatomic changes associated with CRF, the distribution and elimination of intravenous anesthetic agents may be unpredictable. Altered protein binding, a frequent finding in patients with renal disease (12,13), can change free-drug concentration and thereby influence a drug's volume of distribution, rate of clearance, and pharmacodynamic properties. In addition, other pathophysiologic effects of CRF and/or dialysis can modulate drug dis-

tribution and metabolism. Therefore, we designed this study to evaluate the pharmacokinetics of sufentanil in adolescent patients with normal and abnormal renal function.

### Methods

Twelve patients, 10 to 15 years old, who were scheduled for surgical procedures and anesthesia that necessitated invasive monitoring were included in this study. The procedures in Group 1 (control,  $n = 6$ ) included craniotomy (three patients), exploratory laparotomy (two patients), and odontoid resection (one patient). The mean ( $\pm$  SD) age in Group 1 was  $11.7 \pm 3.8$  years and the mean weight was  $44.7 \pm 12.9$  kg. No patient in Group 1 had any evidence of impaired renal function. Mean blood urea nitrogen and creatinine levels in Group 1 were  $10.2 \pm 3.5$  and  $0.6 \pm 0.2$ , respectively. Patients in Group 2 ( $n = 6$ ) had documented CRF requiring either peritoneal dialysis or hemodialysis and were scheduled for kidney transplantation. Their mean age was  $11.8 \pm 1.7$  years, mean weight was  $28.7 \pm 5.7$  kg, and mean blood urea nitrogen and creatinine levels were  $66 \pm 14.6$  and  $8.6 \pm 3.2$ , respectively. The study was approved by our institution's Human Rights Committee, and in-

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formed written consent was obtained from both the patient and a parent.

Anesthesia, induced with thiopental 4 mg/kg and nitrous oxide in oxygen, was maintained briefly with nitrous oxide and halothane until appropriate venous and arterial catheters were inserted and tracheal intubation accomplished. Pancuronium 0.1 mg/kg was given to patients in Group 1 and atracurium 0.5 mg/kg was given in Group 2 to facilitate tracheal intubation, control of ventilation, and prevention of chest wall rigidity. After halothane had been discontinued and the end-tidal concentration had decreased to <0.10%, sufentanil (3–5  $\mu$ g/kg) was infused over 1 minute; nitrous oxide (67%) and oxygen (33%) were continued.

Arterial blood samples for sufentanil analysis were obtained 1, 3, 5, 7.5, 15, 30, 45, 60, 90, 120, and 180 minutes after infusion, or until the time the transplanted kidney was incorporated into the circulation. In some patients in Group 1, additional blood samples were taken for 6 to 24 hours. However, for the sake of comparison, plasma levels only up to 180 minutes were used to estimate the apparent pharmacokinetics. The blood samples were immediately centrifuged, and the plasma decanted, stored, and frozen at  $-60^{\circ}\text{C}$ . Sufentanil concentration was determined with a specific radioimmunoassay. This assay accurately detects 0.5 ng/ml of sufentanil with interassay and intraassay coefficients of variation <5% over the range of concentrations measured. All samples were assayed in triplicate.

The pharmacokinetic data were analyzed by both model-dependent and model-independent methods (14–16). For the model-independent methods the decay curve of sufentanil concentration (C) versus time (t) from 1 to 180 minutes was evaluated. The pharmacokinetic parameters were determined by standard formulas. The area under the concentration curve (AUC) was calculated using the linear trapezoidal rule calculated to 180 minutes; rate of clearance (Cl) was calculated as  $\text{Cl} = \text{dose}/\text{AUC}$ ; apparent volume of distribution at 180 minutes ( $\text{Vd}_{180}$ ) =  $\text{dose} \times \text{AUMC} / (\text{AUC})^2$ , where AUMC is the area under the curve of the first moment, (C – t) (16). The volume of distribution and rate of clearance were indexed to weight. The model-dependent computations were performed using a weighted nonlinear least squares regression program (15). Using standard formulas we calculated the distribution half-life ( $t_{1/2\alpha}$ ) as  $t = 0.693/\alpha$ ; elimination phase half-life ( $t_{1/2\beta}$ ) as  $0.693/\beta$ .

The F-ratio test was applied to the results obtained by fitting the two-compartment open model to the experimental plasma concentration time data. In no

**Table 1.** Pharmacokinetics of Sufentanil in Adolescent Patients (Group 1) with Chronic Renal Failure and in Normal Control Patients (Group 2)

Group	$\text{Vd}_{180}$ (L/kg)	$t_{1/2\alpha}$ (min)	$t_{1/2\beta 180}$ (min)	Clearance ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )
1	$1.65 \pm 0.6$	$2.85 \pm 1.7$	$89.7 \pm 15.7$	$16.4 \pm 6.1$
2	$1.28 \pm 0.62$	$2.5 \pm 0.73$	$76.0 \pm 32.8$	$12.8 \pm 12.0$

Data are means  $\pm$  SD.

Abbreviations:  $\text{Vd}_{180}$ , volume of distribution at 180 minutes;  $t_{1/2\alpha}$ , redistribution phase half-life;  $t_{1/2\beta 180}$ , elimination phase half-life at 180 minutes.

patient was the weighted residual sum of the squares sufficiently reduced ( $P = 0.05$ ) by the addition of a third compartment (17). Residual plots and the goodness of fit confirmed these findings. Both parametric and nonparametric analyses were performed to determine the statistical significance of the pharmacokinetic profiles between the two groups. Statistical significance was assumed for  $P < 0.05$ . The kinetic parameters for model-dependent and model-independent methods of analysis were compared by linear regression. A two-tailed *t*-test for unpaired data was used to compare the mean parameters.

## Results

The plasma concentration decay curve could be described best by a biexponential equation. Table 1 summarizes the pharmacokinetic data for both groups of patients. There was no statistically significant difference in rate of clearance, half-life, or steady-state volume of distribution between the two groups. The values for clearance, apparent volume of distribution ( $\text{Vd}_{180}$ ), and elimination half-life ( $t_{1/2\beta 180}$ ) obtained by both model-independent and model-dependent methods were similar. Although there was no difference in age between the two groups, CRF patients weighed significantly less than the control patients ( $28.7 \pm 5.7$  vs  $44.7 \pm 12.9$  kg).

## Discussion

The pharmacokinetic profile of narcotics can be altered in renal disease (18,19). Because of the pathophysiologic changes associated with renal failure, patients with chronic renal failure frequently have alterations in protein binding, changes in the volumes in which drugs distribute, and changes in the clearance rates in which drugs are eliminated. In a study of the pharmacokinetics of morphine, Chauvin et al. (18) found that patients with CRF had similar

rates of clearance and half-lives but significantly smaller steady-state volumes of distribution, compared with age- and weight-matched control patients. Although CRF did not alter the elimination of unchanged morphine, metabolites of morphine accumulated at higher plasma levels and for longer time periods in the patients with CRF.

Chauvin et al. (19) also studied the pharmacokinetics of alfentanil in adult patients with CRF. The clearance and half-life values for alfentanil were similar in renal failure patients and in normal control patients. In contrast to the smaller steady-state volumes of distribution of morphine in CRF, the steady-state volumes of distribution of alfentanil in CRF patients were significantly larger than those in the control patients. However, when the kinetic parameters for alfentanil were corrected for protein binding, the steady-state volumes of distribution and rates of clearance of unbound drug were similar in CRF and control patients.

There are a few published reports of the elimination and metabolism of sufentanil in humans; however, the role of the kidney in sufentanil elimination has not been defined. As in the studies of morphine and alfentanil by Chauvin et al. (18,19), the data in our study suggest that in adolescent patients with CRF, clearance, apparent volume of distribution, and half-life are similar to those in age-matched control patients, despite the lower weights of CRF patients.

Although we found no statistical difference between the groups with regard to clearance and elimination half-life, these indexes were more variable among the CRF patients. Whether the degree of variability is a consequence of our small sample size, the underlying pathophysiology of CRF, and/or dialysis and its effect on protein binding, or whether the variability represents the occurrence of polymorphic oxidative metabolism is unclear. Although polymorphic oxidative metabolism has been suggested as an explanation for the large variance in the clearance values of alfentanil and sufentanil, it has not been unequivocally demonstrated (20,21). Fyman et al. (22), in a preliminary report of a study of a group of ten patients 28-47 years old who were about to undergo kidney transplantation, found that patients with CRF had similar clearance and half-life values for sufentanil but smaller volumes of  $\beta$ -phase distribution compared with the pharmacokinetic profiles reported by Bovill et al. (3). Fyman et al. (22) in their pharmacokinetic calculations included measurements of plasma sufentanil concentrations obtained after the kidney was revascularized. Nonetheless, their findings regarding clearance and terminal elimination half-life of sufentanil were qualitatively similar to our

results. Differences in the actual sufentanil pharmacokinetic values between the study by Fyman et al. (22) and ours could be related to differences in age and/or severity of the underlying CRF and/or the sampling times.

Our kinetic parameters also differ from the values reported in children by Greeley et al. (5). Although their adolescent patients had sufentanil clearances similar to our control patients, their reported volume of distribution and elimination half-life were two-fold greater. Differences in the pharmacokinetic profile between these two studies of similar aged patients may be related to differences in the underlying disease states (23,24) and to the length of time that the plasma was sampled (25,27). Koren et al. (23) noted that the pharmacokinetic profile for fentanyl in infants and children undergoing corrective procedures for congenital heart defects was affected by both age and the patient's underlying hemodynamic state. The longer sampling times used by Greeley et al. (5) (4-24 hours compared with 3 hours in our study) allow for detection of other compartments and thus may account for the reported larger volume of distribution and the resultant longer elimination half-life. In two patients in our control group, plasma was sampled for 6 hours after sufentanil injection. The longer sampling time results in a similar plasma clearance ( $11.3 \pm 3.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) but the plasma half-life (228 minutes  $\pm$  73) and volume of distribution ( $3.3 \text{ L/kg} \pm 0.35$ ) significantly increased. These calculated values for half-life and clearance are similar to those reported by Greeley et al. (5). We speculated that both the absence of kidney function and the revascularization of the transplanted kidney would influence the kinetics of sufentanil. We therefore elected to limit plasma sampling to the anephric time period. Although the estimate of plasma clearance has approximated that reported for longer sampling times, it appears that our reported elimination half-life and volume of distribution, though descriptive of the clinical situation, may not be truly representative of the drug's terminal disposition. We have thus characterized these pharmacokinetic estimates with a sampling period subscript (e.g.,  $\text{Vd}_{180}$ ).

In conclusion, CRF, with its alterations in fluid and electrolyte homeostasis, does not appear to alter significantly the volume of distribution of sufentanil in adolescent patients. The lack of a significant difference in sufentanil clearance and half-life in adolescents with CRF in the clinical situation that we studied suggests that renal elimination of sufentanil is minimal; nevertheless, the wide variability in clearance and terminal elimination half-life observed in

patients with renal failure means that administration of sufentanil should be individualized.

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## The Temperature of Bupivacaine 0.5% Affects the Sensory Level of Spinal Anesthesia

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STIENSTRA R, VAN POORTEN JF. The temperature of biupvacaine 0.5% affects the sensory level of spinal anesthesia. *Anesth Analg* 1988;67:272-6.

*Three milliliters of plain bupivacaine 0.5% was injected intrathecally in two groups of 20 patients. Group 1 received a solution that had been equilibrated to 37°C, group 2 received a solution that had been equilibrated to 4°C. Patients were kept sitting for 3 minutes after injection. All observations were observer-blind. The differences between segmental*

*levels of sensory loss between groups 1 and 2 (T4 and T9, respectively) and of temperature loss (T3 and T8, respectively) 10 and 20 minutes after injection of bupivacaine were statistically significant. It is concluded that the time needed for thermal equilibration in the cerebrospinal fluid and hence temperature of the injected solution plays an important role in the sensory spread of plain bupivacaine 0.5%.*

Key Words: ANESTHETIC TECHNIQUES—spinal. ANESTHETICS, LOCAL—bupivacaine.

It has been shown that anesthetic solutions in vitro equilibrate with body temperature within 1 to 2 minutes (1,2). Accordingly, it is assumed that the clinically important densities of anesthetic solutions are those measured at 37°C (3). The baricity of a solution is the density of that solution divided by the density of cerebrospinal fluid. By definition, a solution is isobaric if baricity is 1.0000; if baricity is >1.0000, the solution is hyperbaric; if less, it is hypobaric.

The plain solution of bupivacaine 0.5% at a temperature of 4°C has a density of 1.0040 (courtesy of Astra, The Netherlands); because the mean density of cerebrospinal fluid at 37°C is 1.0003 (1,3), the plain solution of 0.5% bupivacaine is slightly hyperbaric. At 37°C, the density of plain bupivacaine 0.5% is 0.9970 (courtesy of Astra, The Netherlands), i.e., the solution is slightly hypobaric. The present study was undertaken to determine if this difference in baricity has any clinical significance.

### Patients and Methods

Forty male patients (ASA I-II) scheduled for urologic surgery under spinal anesthesia were randomly allo-

cated to one of two groups. Each group comprised 20 patients. All patients received 3 ml plain bupivacaine 0.5% while sitting; they were kept in the sitting position for 3 minutes after completion of the intrathecal injection of the solution and were then turned into the supine horizontal position. Patients in group 1 received a solution that had been previously equilibrated in a stove (MELAG Apparate GmbH W-Germany, type 85) to 37°C for at least 1 day. Patients in group 2 received a solution that had been equilibrated in a refrigerator to 4°C for at least 1 day. Syringes used to administer the bupivacaine solution were also equilibrated to 37°C and 4°C, respectively. The study was approved by the Ethical Committee of our institution and oral consent was obtained from all patients.

Premedication consisted of lorazepam 1 mg orally the night before surgery. Before induction of spinal anesthesia 500 ml Ringer's solution were administered by rapid intravenous infusion, followed, after completion of the intrathecal injection, by 500 ml of a plasma expander (Haemaccel) at a slower rate. Dural puncture was performed with the patient in the sitting position at the L3-L4 interspace using a standard midline or paramedian approach and a 25-gauge spinal needle.

Blood pressure and pulse rate were measured before injection ( $T = 0$ ) and at 5-minute intervals after injection for 20 minutes ( $T = 5-20$ ) using an automatic

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Table 1. Characteristics of the Patients Studied

	Group 1 (n = 20)*	Group 2 (n = 20)†	Delta 1-2 (P value)
Age (yr)	63 ± 1.93‡	67 ± 1.95	NS
Length (cm)	175 ± 1.39	175 ± 1.28	NS
Weight (kg)	78 ± 2.01	75 ± 1.46	NS

\*Plain bupivacaine, 37°C.

†Plain bupivacaine, 4°C.

‡Data are mean values ± SEM.

Table 2. Segmental Levels of Loss of Sensation to Temperature (Temp) and Pinprick 10 and 20 Minutes after Injection

	Group 1 (n = 20)*	Group 2 (n = 20)†	Delta 1-2 (P value)
Temp 10' (SEM)	T4 (0.29)‡	T10 (0.51)	<0.002
Temp 20' (SEM)	T3 (0.24)	T8 (0.53)	<0.002
Pinprick 10'	T5 (0.30)	T10 (0.47)	<0.002
Pinprick 20'	T4 (0.26)	T9 (0.48)	<0.002

\*Plain bupivacaine, 37°C.

†Plain bupivacaine, 4°C.

‡Data are mean values ± SEM.

cycling device (Dinamap). ECG was monitored continuously.

Measurements of the levels of sensory changes were made 10 and 20 minutes after injection of the bupivacaine solution. Sensory loss was measured in the anterior axillary line by pinprick using a short-bevelled 25-gauge needle. Temperature loss was measured using a cold bottle containing a frozen salt solution. The segment at which the patient was not capable of recognizing the temperature of the bottle as well as the segment of loss of sensation to pinprick were recorded. Motor blockade was assessed 10 and 20 minutes after injection using a 0-3 scale as described by Bromage (4). All punctures and observations were made by the authors under "observer blind" conditions.

Results are expressed as means ± SEM. Statistical analysis used the Wilcoxon test for matched pairs for intragroup variations and the Mann-Whitney-U test for intergroup comparisons. For comparison of differences in motor blockade between the two groups the  $\chi^2$  test according to Yates was used.  $P < 0.05$  was taken as indicative of statistically significant differences.

## Results

There were no statistical significant differences between the two groups regarding age, height, or

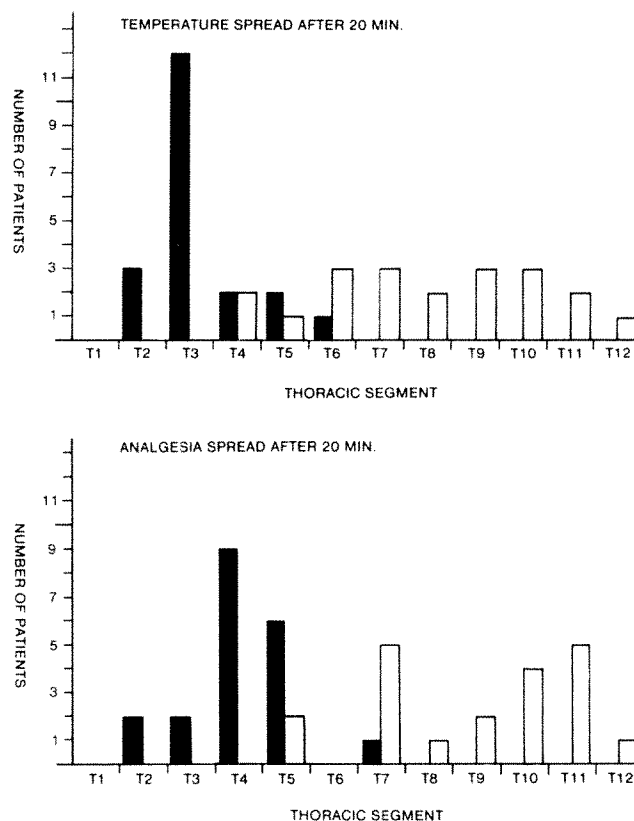


Figure 1. Segmental levels of temperature loss (temperature spread) and loss of sensation to pinprick (analgesia spread) 20 minutes after injection. The horizontal axis shows the thoracic segment at which temperature loss and loss of sensation to pinprick were measured; the vertical axis shows the number of patients. The differences between the two groups regarding temperature and analgesia spread were statistically significant. ■ Group 1: plain bupivacaine, 37°C; □ Group 2: plain bupivacaine, 4°C.

weight (Table 1). The segmental level of temperature loss after 10 minutes was T4 in group 1 and T10 in group 2; after 20 minutes, these levels were T3 and T8, respectively. The segmental level of loss of sensation to pinprick after 10 minutes was T5 in group 1 and T10 in group 2; after 20 minutes these levels were T4 and T9, respectively. The differences in sensory levels between groups were statistically significant at both 10 and at 20 minutes (Table 2). The ranges of levels are shown in Figure 1. The differences in motor blockade between the two groups at 10 and 20 minutes were not significant. The distribution of motor blockade is shown in Figure 2.

Systolic blood pressures decreased in both groups, decreases being significantly below baseline levels after 5, 10, 15, and 20 minutes, the decrease being more pronounced in group 1. There was no significant difference in systolic blood pressures at T = 0 between groups. Differences between decreases in systolic blood pressures in both groups were signifi-

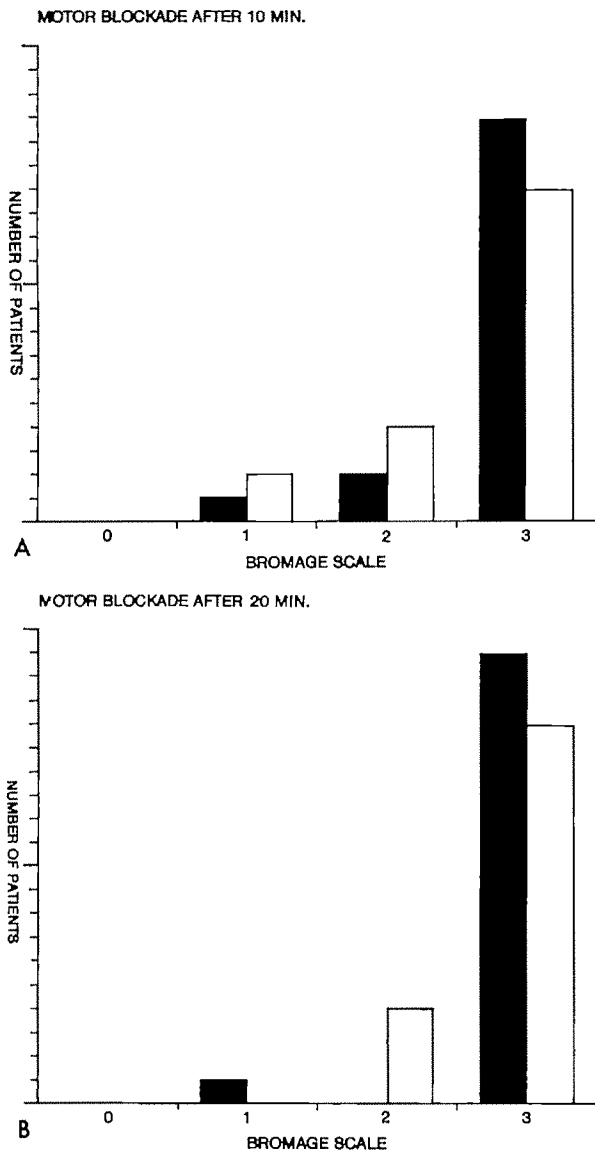


Figure 2. Degree of motor blockade 10 minutes after injection (A) and 20 minutes after injection (B). The horizontal axis shows the Bromage scale: 0 = no motor block; 1 = inability to raise the extended leg; 2 = inability to flex the knee; 3 = complete motor block. The vertical axis shows the number of patients. Differences in motor blockade were statistically not significant. ■ Group 1: plain bupivacaine, 37°C; □ Group 2: plain bupivacaine, 4°C.

cant at T = 10. In three patients in group 1 and one patient in group 2 the decrease in blood pressure necessitated the use of ephedrine. Apart from a significant increase in heart rate at T = 5 in group 1, heart rates did not change significantly; intergroup comparison of the changes in heart rates showed no significant difference. Hemodynamic data are summarized in Table 3.

In one patient in group 2 (analgesia level T12), analgesia was not sufficient and had to be supplemented with nitrous oxide. One patient in group 2 developed postspinal headache, which was successfully treated with an epidural blood patch.

Table 3. Systolic BP (mm Hg) and Heart Rate (beats/min) at Various Times (t) during and after Injection into Subarachnoid Space

	Group 1 (n = 20)*	Group 2 (n = 20)†	Delta 1-2 (P value)
Systolic BP (t = 0)	142 (2.96)‡	137 (3.80)	NS
Systolic BP (t = 5)	128 (3.45) P < 0.001	129 (4.22) P < 0.01	NS
Systolic BP (t = 10)	115 (2.62) P < 0.001	126 (4.14) P < 0.01	<0.01
Systolic BP (t = 15)	118 (2.38) P < 0.001	121 (4.37) P < 0.001	NS
Systolic BP (t = 20)	116 (2.48) P < 0.001	123 (4.26) P < 0.001	NS
Heart rate (t = 0)	77 (4.02)	74 (3.27)	NS
Heart rate (t = 5)	81 (3.45) P < 0.05	75 (3.05) P = NS	NS
Heart rate (t = 10)	78 (3.35) P = NS	75 (3.04) P = NS	NS
Heart rate (t = 15)	77 (4.82) P = NS	74 (2.58) P = NS	NS
Heart rate (t = 20)	73 (4.10) P = NS	74 (2.46) P = NS	NS

\*Plain bupivacaine, 37°C.

†Plain bupivacaine, 4°C.

‡Data are mean values  $\pm$  SEM.

## Discussion

Although the plain solution of bupivacaine 0.5% has been recognized as a suitable agent for spinal anesthesia (5-12), one of the major criticisms of its use for this purpose is the fact that predictability with regard to sensory spread is poor (13-22). Among the factors that affect the distribution of local anesthetic solutions in the cerebrospinal fluid, the baricity of the injected solution is well established (3). Although the plain solution of bupivacaine 0.5% is slightly hypobaric at 37°C, it is generally regarded and used as an isobaric solution (3).

In an attempt to explain the absence of difference in sensory spread between isobaric and hyperbaric solutions of tetracaine, Levin et al. (23) drew attention to the possibility that the time needed for thermal equilibration of a solution injected at room temperature might be a factor of influence. The assumption that injected solutions reach thermal equilibration in the cerebrospinal fluid within 1 to 2 minutes is based on the work of Davis and King (1) and Ernst (2); apart from the high room temperatures (27°C in the former and 23°C in the latter) both studies were in vitro studies. In none of the studies in which plain bupivacaine 0.5% was used was temperature of the injected solution controlled. As is shown in this study, injecting bupivacaine 0.5% at 37°C not only results in a significantly higher cephalad spread,



but also reduces the variability of sensory spread considerably, as is shown by a relatively small SEM of 0.3.

The fact that the cold solution of 4°C changes from initially slightly hyperbaric to slightly hypobaric during thermal equilibration in the cerebrospinal fluid explains the lower cephalad spread; individual variation in the time needed for thermal equilibration could well explain the greater variability in sensory spread seen with the cold solution. This implies that the time needed for thermal equilibration in the cerebrospinal fluid is an important factor in determining cephalad spread when using plain bupivacaine. It seems reasonable to assume that in most clinics the temperature of the injectate will be the same as room temperature. Because the time needed for thermal equilibration is inversely related to the temperature of the solution, room temperature itself or the temperature of the place of storage of the solution becomes an important factor. It stands to reason to assume that the ensuing levels of sensory blockade after injecting bupivacaine 0.5% at room temperature will be somewhere between those seen with solutions of 4°C and 37°C. The fact that room temperature will be influenced by geographic location and by the time of year might explain, together with individual variation in the time needed for thermal equilibration, the great variability of sensory spread of plain bupivacaine solutions as seen in the literature.

The decrease in systolic blood pressure was greatest in group 1, as might be expected because of higher cephalad spread, although statistical analysis showed the differences to be significant only at  $T = 10$ . When Bonferroni's procedure is applied this difference at  $T = 10$  remains significant. Considering the data, we believe that the lack of significance at  $T = 5$ ,  $T = 15$ , and  $T = 20$  should be explained by a type II error being made due to considerable variation in blood pressures.

Apart from a significant increase at  $T = 5$  in group 1, the heart rates showed no significant changes; when Bonferroni's procedure is applied, the increase in heart rate at  $T = 5$  in group 1 loses significance; the conclusion that it involves a spurious statistical significance seems therefore warranted. As can be seen from Figure 2, there were no major differences in motor blockade; in all patients motor blockade was adequate for surgery.

In conclusion, under the conditions of the present study the time needed for thermal equilibration in the cerebrospinal fluid and hence the temperature of the bupivacaine 0.5% solution is an important factor in determining sensory spread. When using a solution that has been equilibrated previously to 37°C, predict-

ability of the ensuing level of analgesia is good. In case a high level of sensory blockade using bupivacaine 0.5% is desired, the solution should be equilibrated to 37°C.

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## Clinical Reports

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# Nerve Injury and Musculoskeletal Complaints after Cardiac Surgery: Influence of Internal Mammary Artery Dissection and Left Arm Position

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and J. Edmond Charlton, MB, BS, FFARCS

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**Key Words:** COMPLICATIONS—nerve injuries.  
NERVES—injuries. ANESTHESIA—cardiovascular.

Upper extremity nerve injury after cardiac surgery has been reported in six prospective studies (1-6). The incidence of injury ranged from 1.9 to 18.3% (Table 1). The brachial plexus was involved in 80% of cases. Possible causes include penetration injury with first rib fractures (2,3), needle trauma during insertion of internal jugular catheters (5,7,8), watershed infarcts (9), and stretch or compression injuries associated with sternal retraction (3,5), positioning (10,11), or arterial pressure monitoring (8,12). The purpose of this study was to determine prospectively whether dissection of the internal mammary artery (IMA) and position of the left arm influenced the frequency of neurologic dysfunction and musculoskeletal complaints after cardiac surgery.

## Materials and Methods

Two hundred consecutive adults scheduled for medial sternotomy and cardiopulmonary bypass were studied. No written informed consent was considered necessary because there was no randomization and no deviation from the normal intraoperative routine by the five surgeons and seven anesthesiologists involved. This study was approved by the Hospital Quality Assurance Committee.

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For convenience in presentation of data the patients were classified into four groups: Group A—left arm abducted 90°, left internal mammary artery (IMA) harvest; Group B—left arm abducted 90°, no IMA harvest; Group C—left arm at side, left IMA harvest; Group D—left arm at side, no IMA harvest. When the left arm was abducted, the elbow was extended and the forearm supinated. Care was taken to pad the ulnar nerve at the elbow, to limit abduction to no more than 90°, and to elevate the arm slightly above the plane of the operating room table. The right arm was always adducted to the patient's side. Care was taken not to pull the adducted arms and shoulders caudally. The arms were held against the patient by the use of draw sheets that extended above the elbow.

Five physician assistants examined the patients and completed a detailed questionnaire for every patient during the patient's first return visit 1 month postoperatively. Only those patients for whom full intra- and postoperative data were available were included in the analysis. Musculoskeletal complaints were defined as pain and limitation of motion in the arms, shoulders, or back which were not present preoperatively and which required narcotic analgesia (acetaminophen with codeine phosphate). Brachial plexus injury was defined as the appearance of numbness, dysesthesia, or loss of function in the arm or forearm or in the distribution of more than one peripheral nerve of the hand. A more distal peripheral nerve injury was considered when the deficit was confined to digits innervated by a single nerve.

All patients underwent nonpulsatile cardiopulmonary bypass with membrane oxygenation and moderate hypothermia. Two-inch 20-gauge nontapered Teflon left radial or brachial arterial catheters were inserted. The left brachial artery was used in 16



**Table 1.** Incidence of Upper Extremity Nerve Injury after Cardiac Surgery in Prospective Studies

Source	Number of cases	Number with nerve injury (%)
Keates et al. (1)	529	10 (1.9)
Vander Salm et al. (2)	180	33 (18.3)
Vander Salm et al. (3)	120	18 (15.0)
Sotaniemi (4)	100	12 (12.0)
Hanson et al. (5)	531	32 (6.1)
Shaw et al. (6)	312	30 (9.6)
Total	1772	135 (7.6)
This study	162	16 (9.9)

**Table 2.** Patient Characteristics\*

	Group			
	A	B	C	D
Age (yr)	59.4 (9.1)	61.7 (10.1)	56.5 (8.0)	60.6 (10.7)
Weight (kg)	79.0 (11.5)	72.2 (13.7)	80.5 (9.1)	73.7 (8.4)
Male:female ratio	58:9	27:21	30:2	10:5
Time of examination (days)†	31.0 (10.9)	33.5 (7.6)	34.2 (11.8)	31.7 (6.0)

\*Values expressed as mean (sd).

†Postoperative day on which interview and examination for musculoskeletal complaints and upper extremity nerve injury were performed.

patients after unsuccessful attempts at the ipsilateral radial site. Either anterior or high central approaches to the right internal jugular vein (terminology of Defalque [13]) were used to insert pulmonary artery catheters through 8.5F sheaths in all patients.

Parametric data were analyzed by analysis of variance. Nonparametric data and group frequencies were compared using  $\chi^2$  contingency tables.  $P < 0.05$  was considered to represent statistical significance.

## Results

Complete data were available for 162 patients (81%). Demographic data are presented in Table 2. The male:female ratio was greater in groups A and C because the smaller IMAs in females were often considered unsuitable for grafting. The weight differences reflect the differences in the sex ratio. There were no associations of injury with age, sex, weight, anesthesiologist, or surgeon. Patients cared for by one anesthesiologist had both arms adducted. The preference of all other anesthesiologists was to abduct the left arm.

Twelve of the 16 upper extremity nerve injuries observed involved the brachial plexus: 7 were left-sided, 4 were right-sided, and 1 was bilateral. The four peripheral nerve injuries were on the left side: three

**Table 3.** Distribution of Thoracic Musculoskeletal Complaints and Upper Extremity Nerve Injury after Cardiac Surgery

Group	Left arm	IMA	Number of patients		Nerve injury	
			Total	M-S complaints	Left	Right
A	90°	yes	69	28 (41)	7* (10)	3* (4)
B	90°	no	49	11 (22)	3 (6)	0 (0)
C	0°	yes	30	11 (37)	2 (7)	2 (7)
D	0°	no	14	0 (0)	0 (0)	0 (0)

Abbreviations: IMA, harvest of internal mammary artery; M-S, musculoskeletal; nerve injury—upper extremity nerve injury. Percent incidences are in parentheses.

\*One patient with bilateral injury counted both as left and right. Difference in M-S complaints between A + C and B + D is statistically significant. Difference in nerve injury is not significant.

involved the ulnar nerve, one the median nerve. The brachial artery was not cannulated in these four patients. The lower trunk, medial cord, or ulnar branch of the brachial plexus was involved in 15 of the 16 upper extremity nerve injuries. None of the patients felt that they had significant functional disability. The male:female ratio of the injured patients was 13:3.

The distribution of injuries (Table 3) indicates that 39% of patients with IMA grafts (Groups A and C) had musculoskeletal complaints and/or neurologic dysfunction as compared with 17% without IMA grafts (Groups B and D). This difference was statistically significant. However, when upper extremity nerve injuries alone were compared, there were no differences attributable to IMA dissection.

Comparison of Groups A and B with Groups C and D revealed no differences in musculoskeletal complaints or neurologic dysfunction related to left arm position. There appeared to be a trend toward an increase in nerve injury related to abduction of the left arm and subsequent harvest of the IMA, but statistical significance was not achieved.

One anesthesiologist (Groups C and D) recorded the arterial trace during chest retraction for the IMA harvest. Loss of arterial trace, which has been previously reported (14), occurred in 4 of 47 patients (8.5%). One of these four had significant interscapular pain but none suffered upper extremity nerve injury.

## Discussion

The 9.9% incidence of upper extremity nerve injury in this study is similar to that in several previously reported prospective studies (see Table 1). Like Vander Salm et al. (2), we found that left arm position did not influence injury. In 61% of patients in this

study IMA dissections were performed. There was no correlation between this procedure, left arm position, and brachial plexus injury. Thus two maneuvers that can stretch the brachial plexus did not appear to predispose it to injury (2,5).

Placement of an internal jugular cannula has been implicated as a cause of brachial plexus injury after cardiac surgery (5,7). Despite the fact that right internal jugular catheters were inserted in all our patients, the majority of nerve injuries occurred on the left side. It has been reported that 10% of internal jugular catheterizations produce paresthesiae (15). Because the incidence of persistent paresthesiae after brachial plexus block has been reported as varying between 1.4 and 5.6% (16), the expected incidence of nerve injury associated with internal jugular catheterization would be 0.56% or less. Use of larger needles with an A bevel (16) might increase the expected incidence closer to the 2.5% observed in this study on the side ipsilateral to the internal jugular cannula. Nonetheless, insertion of central lines is not the major cause of upper extremity nerve injury.

This study was not designed to establish the time course of the neurologic injuries. We did not look for, and patients did not complain of, these injuries during their immediate postoperative hospitalization. Failure to diagnose injuries associated with relatively minor functional impairment is not unique to our institution (17). Longitudinal studies suggest these injuries are apparent in the first week, perhaps intensify in the second and third weeks, and resolve with 6 months. In a few patients the deficits persist beyond 1 year (1,5-7,16).

Vander Salm et al. (2,3) have documented that median sternotomy can cause first rib fractures and that fractured first ribs can penetrate the brachial plexus. They propose a mechanism for nerve injury that satisfies the observation in all studies that the predominant lesion involves the lower trunk (C8-T1), inferior division, medial cord, or ulnar branch of the brachial plexus: "... increasing amounts of nerve injury occur from increasing amounts of first rib displacement, with severe injury caused by rib fracture" (3). Because the standard chest x-ray film is an insensitive method of detecting first rib fractures, special oblique views must be utilized (3).

In summary, we found a 10% incidence of upper extremity nerve injury after cardiac surgery, an incidence not influenced by arm position, IMA dissection, or internal jugular vein catheterization. Surgical manipulations may be the cause of most upper extremity nerve injury in this setting, but x-ray documentation of first rib fracture and nerve conduction studies are necessary to support this contention. We

also demonstrated an association between musculoskeletal complaints and harvest of the IMA. Patients with these symptoms were still requiring narcotic analgesia 1 month after their surgery.

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## Postoperative Arterial Oxygen Saturation in the Pediatric Population during Transportation

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**Key Words:** ANESTHESIA—pediatric. OXYGEN—saturation.

Hypoxemia ( $\text{Sao}_2$  90%,  $\text{Pao}_2$  58 mm Hg) in the recovery room (RR) is well documented in both the pediatric (1) and adult (2) population. The possibility of hypoxia during transport from operating room (OR) to RR was examined by Tyler et al. (3) in the adult population; they reported that 35% of their patients were hypoxic and 12% severely hypoxic ( $\text{Sao}_2 < 85\%$ ,  $\text{Pao}_2$  50 mm Hg). They attributed this high incidence of hypoxemia to obesity,  $\text{N}_2\text{O}$  diffusion, and decrease in functional residual capacity (FRC) below closing capacity resulting in ventilation/perfusion imbalance. However, we know of only one other report studying the pediatric population for oxygen desaturation ( $\text{Sao}_2$ ) during transport from OR to RR (4).

To study the pattern of  $\text{Sao}_2$  in healthy pediatric patients during transport from OR to RR has been made simple by the availability of the noninvasive pulse oximeter (Nellcor). This tool is easy to use, gives continuous oxygen saturation readings and, above all, has good correlation with arterial samples (5). We used this simple, widely accepted device to monitor desaturation in the healthy pediatric population during transport from OR to RR.

### Methods

Informed consent from parents was obtained following the institutional guidelines on human experimentation. 60 ASA I and II patients between 1 month and 14 years of age were entered into the study. Patients were classified into three subgroups: group 1, 0-6

months of age ( $n = 10$ ); group 2, 7-12 months of age ( $n = 10$ ); and group 3, 13 months-14 years of age ( $n = 40$ ). These patients underwent elective outpatient surgery of various durations. The distribution of the various types of surgery according to group is in Table 1. The duration of anesthesia for each group is displayed in Table 2. No premedication was given and none of the patients received any regional block (caudal) for postoperative pain relief.

All patients in group 1 and group 2 were induced by inhalational anesthesia. In group 3, in addition to the mask, intravenous thiopental or rectal brexital were also used for induction. Eight patients also received atracurium. Anesthesia was maintained with oxygen, nitrous oxide, and halothane. There was no difference in the maintenance concentration of halothane between the three groups; the latter did not exceed 1.5% inspired concentration. The Mapleson D partial rebreathing circuit with controlled or assisted ventilation was used on all patients. Muscle relaxants were reversed with atropine 0.03 mg/kg and neostigmine 0.06 mg/kg. Adequacy of muscle relaxant reversal was tested clinically and by peripheral nerve stimulator. None of the patients received any narcotics during the case. At the end of the procedure, after extubation, or at the end of mask anesthesia, 100%  $\text{O}_2$  was given for 3 minutes. The oxygen was then discontinued and the patients moved to the RR in the left lateral position, as is done routinely at our institution to prevent airway obstruction and to minimize risk of aspiration.  $\text{Sao}_2$  was measured by securing the pulse oximetry sensor on the toe or finger of the patient during transport from OR to RR. All the patients had a temperature above 36°C.

Only one data point was collected for each patient, which represents the lowest  $\text{Sao}_2$  occurring during transport. Transportation lasted 120-180 seconds and was consistent in this range because of our physical facilities and the time required to move and position the child on the stretcher. On arrival in the RR all

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**Table 1.** Type of Surgery According to Group

Type of surgery	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 40)
Eye	4	3	11
Ear	0	2	15
Urology	2	3	6
Hernia	4	2	8

**Table 2.** Duration of Anesthesia in Minutes

	Group 1	Group 2	Group 3
Mean	56.5	49.5	48.12
SD	±29.3	±33.45	±36.99

**Table 3.** Sao<sub>2</sub> during Transport from OR to RR

	Minimum value	Maximum value	Mean	SEM
Group 1 (0-6 months old, n = 10)	82.0	93.0	88.1*	1.20
Group 2 (7-12 months old, n = 10)	85.0	97.0	91.8*	1.0
Group 3 (13-14 years old, n = 40)	89.0	100.0	93.3*	0.47

\**P* < 0.0001.

patients were given O<sub>2</sub> and the study was terminated. Eight patients who were coughing or remained intubated or on whom the sensor came apart during transport were excluded from the study.

Data obtained were first analyzed using one-way analysis of variance. Then Tukey's Studentized Range test was used to determine which group was significantly different. *P* < 0.05 was considered statistically significant.

## Results

Results are shown in Table 3. All patients had adequate airway and ventilation during their transportation as judged by air movement through the mouth and/or nostrils and by observation of chest movement and by the precordial stethoscope.

Sao<sub>2</sub> was 100% in all patients before moving from the OR. Mean Sao<sub>2</sub> during transport for all patient groups was 93.5 ± 0.55% with a range of 82-100%. Mean saturation ranged from 88.12 ± 1.2% in group 1; 91.8 ± 1.0% in group 2, and 93.39 ± 0.47% in group 3. The analysis of variance revealed significant differences among the three group means.

Difference between mean saturations for group comparison was highest between groups 1-3 (7.29) followed by 1-2 (3.70) and 2-3 (3.59). All values are significant at the 0.05 level. The duration of anesthesia in the three groups is compared in Table 2. There was no statistically significant difference among the groups.

## Discussion

In spite of 3 minutes' postanesthetic oxygenation, most pediatric patients desaturate rapidly during transfer to the RR. This desaturation is most notable in the 0-6 month age group, followed by the 7-12 month age group and least in the 13 month-14 year age group. We have considered various mechanisms potentially responsible for this occurrence.

Several aspects of infant physiology may explain marked desaturation seen in the youngest infants. Four patients in group 1 were only 1 month old. At this age the concentration of fetal hemoglobin (Hb F) is 50%, declining to 10-15% by 4 months. We did not directly examine the role of Hb F on tissue oxygen supply, but some assumptions can be made on the basis of available data. In the presence of Hb F, tissue oxygen availability is diminished as the Hb dissociation curve is shifted to the left. Concurrently, during the first 6 months of life, oxygen consumption reaches its first peak. The Hb dissociation curve does not change under anesthesia unless acid-base homeostasis is radically upset. Thus in these four patients postoperative oxygen saturation does not represent the same tissue oxygen availability as in older children with adult type hemoglobin. Potentially, younger children are at worst risk from hypoxemia than older children.

Halothane may contribute to transient postoperative desaturation in a variety of ways, most notably through muscle fatigue. During and after halothane anesthesia, chest wall expansion is altered through intercostal muscle fatigue and inhibition, resulting in rib cage retraction and the unopposed action of the diaphragm. The combination of these factors under halothane anesthesia distorts the chest wall causing lower lung volumes. This effect is most significant in young infants (6,7).

A less likely factor would be a difference in body stores of halothane among the three groups. Maintenance halothane concentrations were identical in all three groups, not exceeding 1.5% inspired concentration. The only difference occurred during induction. Groups 1 and 2 were induced using halothane with inspired concentration reaching 3%. However, this

brief duration of induction is unlikely to contribute significantly to body halothane stores. In addition, faster elimination in these groups is likely to offset any such effect. Also, there was no significant difference in the duration of anesthesia among the three groups—another possible cause of halothane tissue buildup.

The type of surgery cannot be responsible on its own for postoperative hypoxemia. Although there were twice as many inguinal herniorrhaphies in group 1 as in groups 2 and 3 (see Table 1), the other six patients in this group showed similar desaturation without pain-related abdominal splinting causing diminished ventilation.

The infant's pulmonary physiology is different in many respects from that of older children and these differences make him or her more prone to hypoxia. Instability of the small airways with closure within the tidal volume due to lesser elastic recoil and diminished distensibility of the lungs occur in infancy even without the effect of general anesthesia (8). Under general anesthesia, functional lung capacity is markedly reduced in infants and children, resulting in airway closure and increase in A-aDO<sub>2</sub> (9) that may well continue in the postoperative period during transport from OR to RR.

Barbiturates, either rectal methohexital or IV thiopental were only utilized in group 3. Saturation in this group was least affected.

Narcotics significantly depress the ventilatory response to hypoxemia as well as hypercapnia and may cause hypoxemia secondary to hypoventilation (10). Though none of our patients received narcotics, results might have been different had they received narcotics in addition to inhalation anesthesia. Trace concentration of inhalation anesthetic may depress hypoxic drive in these patients (11), resulting in respiratory depression and further hypoxemia.

Traditionally, healthy, low-risk pediatric patients are transported from the OR to RR without supplemental oxygen. There has been no case report in the literature implicating this short period of hypoxemia in the development of any irreversible cardiovascular

or central nervous system effects. However, such potential does exist because any of these pediatric patients may have airway obstruction, prolonged coughing, vomiting, or respiratory depression during transportation.

This discussion attempts to elucidate the various possible mechanisms that may be responsible for transient postoperative hypoxemia. Differences in infant physiology appear to be the main causative factor. Pulse oximetry is a simple method to quantitate the resulting desaturation. Rapid transport to the RR and/or supplemental oxygen is recommended to avoid potential hypoxia in the very young.

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## Placement of Nasogastric Tubes and Esophageal Stethoscopes in Patients with Documented Esophageal Varices

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**Key Words:** GASTROINTESTINAL TRACT—  
ESOPHAGUS—varices. LIVER—esophageal varices.

Hemorrhage from dilated esophageal varices represents the most serious complication of portal hypertension secondary to chronic liver disease. Thirty percent of cirrhotic patients with demonstrated esophageal varices will bleed, and 60% of those patients who have hemorrhaged once will rebleed massively within a year (1).

As anesthesiologists, we are frequently confronted with the patient with known hepatic disease, portal hypertension, or history of esophageal varices. There are case reports in the surgical and anesthesia literature of instrumentation of the esophagus causing catastrophic esophageal variceal hemorrhage. Zollinger and Nick (2) have stated that nasogastric instrumentation is "routinely used except when physical signs of cirrhosis are recognized." Other writers have supported this view (3,4). There have also been studies in the medical literature of variceal rupture during gastroscopic or esophagoscopy procedures (5,6). Because of these reported complications, clinicians have felt reluctant to place nasogastric tubes and esophageal stethoscopes in patients with known esophageal varices. Despite these reports, Lopez-Torres and Waye (7) studied 24 patients who were alcoholic cirrhotics with esophageal varices and recent episodes of upper gastrointestinal bleeding and found no increased incidence of bleeding secondary to esophageal instrumentation. Their conclusion was that avoidance of esophageal instrumentation in patients with chronic liver disease because of fear of hemorrhage may not be justified.

In support of this view, we present our data derived from patients with hepatic pathology who

underwent orthotopic liver transplantation at our institution from March 1985 to March 1987. This study was approved by the Mayo Clinic Human Rights Committee and the Institutional Review Board.

### Methods

During the period of study, 75 patients with end-stage hepatic disease underwent orthotopic liver transplantation. These patients underwent extensive preoperative evaluation including coagulation profiles and esophagogastrosocopy.

During esophagogastrosocopy each patient was examined for the presence of esophageal varices and, if found, the varices were graded according to severity. This grading system, described by Baker et al. (1), is based on variceal fundamental color, form of varices, size, and location.

Grade 0—No varices present.

Grade I—One or more varices <4 mm in diameter, <4 cm in extent.

Grade II—One or more varices 4–10 cm in extent, enlarged, tortuous.

Grade III—One or more large-sized varices extending >10 cm of extent of esophagus.

The preoperative records of each patient were also examined for any previous history of upper gastrointestinal tract bleeding, esophageal pathology, or esophageal variceal sclerosal therapy. All patients underwent extensive coagulation testing to determine the presence and/or extent of coagulopathy secondary to liver disease. Preoperative tests included IVY bleeding time, prothrombin time, activated partial thromboplastin time, and platelet count.

All patients undergoing liver transplantation during this period of study has rapid-sequence induction of anesthesia with thiopental 3–5 mg/kg followed by succinylcholine 1.5 mg/kg. After orotracheal intubation, an 18F Standard Salem sump nasogastric (NG)

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**Table 1.** Primary Diagnoses of Patients Undergoing Orthotopic Liver Transplantation

Diagnosis	No. of patients
Primary sclerosing cholangitis	27
Primary biliary sclerosis	21
Chronic active hepatitis	11
Cryptogenic cirrhosis (non-A, non-B hepatitis)	6
Subacute hepatic failure	3
Fulminant hepatitis	2
Biliary atresia	1
Atrophic liver secondary to portal hypertension	1
Biliary hypoplasia	1
Primary bile duct cancer	1
Hepatocellular carcinoma	1
Total	75

tube and 24F Sheridan Sonatemp esophageal stethoscope were blindly placed with Americaine anesthetic lubricant. All of the Salem sump NG tubes were connected to either continuous or intermittent suction throughout the intraoperative period and the presence or absence of blood in the aspirate was recorded.

## Results

The 75 patients presented with multiple etiologies of primary hepatic disease. Table 1 reports the distribution of diagnoses in this patient population. All patients included in this study were considered to have end-stage hepatic disease. Many patients were in severe hepatic failure at the time of presentation as manifested, for example, by hepatic encephalopathy, hepatorenal syndrome, profound elevation of liver function tests, and hemodynamic instability. No patient in this study was actively bleeding from a gastrointestinal source at the time of surgery. Because of the wide range of clinical severity at the time of the transplant procedure, we feel this patient population was fairly representative of patients with chronic liver disease, not actively bleeding, who may present to the operating room for other surgical procedures.

Table 2 indicates the preoperative coagulation status of these patients. This patient population was consistently found to have a prolonged IVY bleeding time, prothrombin time, and activated partial thromboplastin time, as well as low platelet counts secondary to their chronic liver disease. The coagulation indexes of patients with chronic active hepatitis and cryptogenic cirrhosis were, as expected, more abnormal than were those indexes in patients with other types of liver disease. Also as expected, the prothrombin time (a measure of the extrinsic system of coagulation) was more consistently abnormal than

the activated partial thromboplastin time (a measure of the intrinsic system). The high amount of factor VIII produced in many patients with chronic liver disease is involved in the intrinsic coagulation pathway and may partially compensate for the low concentration of other coagulation factors produced. Therefore, the activated partial thromboplastin time is usually less prolonged than the prothrombin time in this patient population.

Table 3 shows the results of our investigation. Out of 27 patients with primary sclerosing cholangitis, 24 (88.9%) had documented varices and 14 of these 24 patients (58.3%) had a history of previous upper gastrointestinal bleeding. In patients with primary biliary cirrhosis, 16 of 21 (76.2%) had varices, but only 6 of these 16 (37.5%) had a previous history of bleeding. All patients in our series with chronic active hepatitis had documented varices present, and 5 of 11 (45.5%) of these had previously bled.

Twelve of 75 patients (16%) had sclerosing therapy performed within 3 months before liver transplantation. These were all in patients with a history of previous upper gastrointestinal bleeding. Also noted was that in patients having documented grade II or III varices a 65.8% incidence of previous upper gastrointestinal bleeding was seen. Therefore, despite a significant percentage of patients with documented esophageal varices, significant coagulopathies, and a high incidence of previous upper gastrointestinal bleeding, no patient in our series developed hemorrhage as a result of instrumentation of their esophagus with a nasogastric tube or esophageal stethoscope. Although our observed proportion of cases with variceal hemorrhage was 0%, the 95% confidence interval for the true proportion of variceal hemorrhage is from 0 to 4.8%.

## Discussion

In our series of 75 patients undergoing orthotopic liver transplantation, we found no incident of variceal bleeding secondary to blind placement of nasogastric tubes and esophageal stethoscopes despite documented endoscopy-proven varices and the presence of coagulopathies. Our patient population did not have active variceal bleeding at the time of surgery and therefore is not representative of patients having emergency surgery for active variceal hemorrhage. Rather, this study represents a population of patients with chronic liver disease and objectively graded esophageal varices undergoing esophageal instrumentation for monitoring purposes during a surgical procedure. From this study, we can state that using the 95% confidence interval, a <4.8% incidence of variceal hemorrhage from instrumentation can be expected.

Table 2. Preoperative Coagulation Indexes in Patients Undergoing Orthotopic Liver Transplantation

Primary diagnosis	IVY bleeding time (normal 1-6 min)*	Platelet count (normal 185-450,000)*	Prothrombin time (normal 10.9-12.8 sec)*	Activated partial thromboplastin time (normal 25-41 sec)
Primary sclerosing cholangitis ( <i>n</i> = 27)	5.5 ± 2.7	207.1 ± 161.4	22.4 ± 5.6	36.8 ± 5.7
Primary biliary cirrhosis ( <i>n</i> = 21)	5.5 ± 3.6	213.0 ± 134.0	20.4 ± 1.9	34.3 ± 5.5
Chronic active hepatitis ( <i>n</i> = 11)	8.9 ± 4.7	95.1 ± 53.3	23.6 ± 2.6	41.8 ± 9.7
Cryptogenic cirrhosis ( <i>n</i> = 6)	7.0 ± 5.3	106.2 ± 61.4	35.7 ± 10.9	55.5 ± 24.6
Cancer ( <i>n</i> = 2)	4.9 ± 1.5	408.0 ± 356.4	22.0 ± 4.2	30.0 ± 5.7
Other ( <i>n</i> = 8)	6.4 ± 2.3	125.6 ± 45.7	44.4 ± 26.5	65.9 ± 35.1

\*Values are means ± SD.

Table 3. Data of Upper Gastrointestinal (GI) Endoscopy Results and Previous Gastrointestinal Bleeding Histories

Primary diagnosis	No varices			Grade I			Grade II			Grade III		
	No. of patients	No. with previous GI bleeding history	<sup>a</sup> PST	No. of Pts	No. with previous GI bleeding history	<sup>a</sup> PST	No. of Pts	No. with previous GI bleeding history	<sup>a</sup> PST	No. of patients	No. with previous GI bleeding history	<sup>a</sup> PST
Primary sclerosing cholangitis ( <i>n</i> = 27)	3	0	0	7	3	0	10	4	3	7	7	1
Primary biliary cirrhosis ( <i>n</i> = 21)	5	0	0	6	0	0	7	3	1	3	3	1
Chronic active hepatitis ( <i>n</i> = 11)	0	0	0	6	0	0	3	2	1	2	2	2
Cryptogenic cirrhosis ( <i>n</i> = 6)	0	0	0	2	1	0	2	2	1	2	2	2
Cancer ( <i>n</i> = 2)	2	0	0	0	0	0	0	0	0	0	0	0
Other ( <i>n</i> = 8)	4	0	0	2	0	0	2	0	0	0	0	0
Totals ( <i>n</i> = 75)	14	0	0	23	4	0	24	11	6	14	14	6

<sup>a</sup>PST = prior sclerosal therapy.

In summary, as anesthesiologists we are faced with the decision in patients with chronic liver disease of whether to place esophageal stethoscopes and/or nasogastric tubes for diagnostic, therapeutic, or monitoring purposes. In many of these patients we avoid their use because of the fear of initiating variceal bleeding. Despite reports in the literature of massive gastrointestinal hemorrhage after instrumentation, we experienced no incident of variceal bleeding in this series of patients. In spite of these results, we believe care should be exercised in placement of nasogastric tubes and esophageal stethoscopes in patients with esophageal varices, especially in those with coagulopathies or a previous history of upper gastrointestinal bleeding.

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## Continuous Intravenous Midazolam Infusion for Sedation in the Pediatric Intensive Care Unit

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**Key Words:** HYPNOTICS, BENZODIAZEPINES—midazolam. ANESTHESIA—pediatric.

Sedation of intubated spontaneously breathing children in the pediatric intensive care unit is desirable yet often difficult to achieve. A technique for providing consistent sedation in this situation has not been identified. Midazolam is an imidazobenzodiazepine with rapid onset of action and short duration that has been used successfully for sedation in pediatrics (1-4). The pharmacokinetics of midazolam allow the drug to be used as a continuous intravenous infusion (5-11). Continuous midazolam infusion with concurrent morphine sulfate infusion has been shown effective in mechanically ventilated children after cardiac surgery (10,11). Combining a narcotic aides in sedation but adds undesirable side effects inherent to opioids. The purpose of this paper is to report on the use of midazolam for sedation in intubated spontaneously breathing children in the absence of opioids or other sedatives.

### Case Reports

Four patients admitted to the pediatric intensive care unit, ranging in age from 2 months to 3.5 years, are discussed. All patients were described as agitated by both the nursing staff and the physician team. The midazolam sedation was initiated by a bolus with 0.2 mg/kg IV, followed by a continuous infusion beginning at  $0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ .

#### Case 1

A 9.1-kg, 14-month-old male diagnosed with subglottic stenosis secondary to acute viral laryngotracheo-

bronchitis was intubated and initially mechanically ventilated. Agitation was treated with a midazolam bolus followed by continuous infusion. Three days after admission, the patient was extubated in the operating room but had to be reintubated with a smaller endotracheal tube because of persistent obstruction. Two days later, he was successfully extubated in the operating room, and the midazolam infusion was discontinued. The duration of the midazolam infusion was 116 hours, of which 48 hours were with spontaneous respiration.

#### Case 2

A 20.0-kg, 3.5-year-old male diagnosed with subglottic stenosis secondary to acute viral laryngotracheobronchitis who was intubated at an outside institution. On arrival at our institution, the patient was thrashing wildly in bed and required four-point restraints. Hypoxia was ruled out. Midazolam bolus followed by continuous infusion provided adequate sedation. Four days after admission, an attempt to extubate the patient in the operating room failed because of persistent upper airway obstruction. A smaller endotracheal tube was inserted and steroids were given to decrease inflammation. Three days later, he was successfully extubated in the operating room and the midazolam infusion was discontinued.

#### Case 3

A 4.8-kg, 5-month-old premature (32 week gestational age) male was admitted with subglottic stenosis secondary to acute viral laryngotracheobronchitis. The patient was intubated and initially mechanically ventilated. Agitation was treated with midazolam bolus followed by a continuous infusion. Steroids were administered and the patient was successfully extubated in the operating room. The infusion was continued for 23 hours after extubation to prevent agitation, which might have worsened the patient's respiratory status.

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Table 1. Patient Data

	Case 1	Case 2	Case 3	Case 4
Age	14 months	3.5 years	5 months	2 months
Sex	Male	Male	Male	Male
Weight (kg)	9.1	20.0	4.8	3.06
Loading dose (mg)	1.82	4.0	0.96	0.61
Total dose of infusion (mg)	27.4	147.0	5.404	2.916
Duration of infusion (hr)	116	194	42	37
Percent of time on infusion with spontaneous respirations (%)	41.3	100.0	54.7	2.7
Dose range ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	0.4-0.6	0.4-1.2	0.1-0.5	0.2-0.8
Average dose ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	0.432	0.631	0.447	0.387
Respiratory rate range during infusion (breaths/min)	15-44	20-32	60-76	30-78
Respiratory rate after infusion (breaths/min)	28-46	16-30	40-60	60-80
Pco <sub>2</sub> range during spontaneous respiration (mm Hg)	29-41	42-47	31-44	27-42
%O <sub>2</sub> saturation range during infusion	94-100	99-100	96-100	93-100

### Case 4

A 3.06-kg 2-month-old premature (37 weeks gestational age) male diagnosed with bronchiolitis secondary to respiratory syncytial virus was intubated and initially mechanically ventilated. After intubation, the child was extremely agitated. An intravenous bolus followed by a continuous infusion of midazolam was begun. He was extubated 37 hours later and did well.

### Results

See Table 1 for patient data. ECG, respirations, and oxygen saturation by pulse oximetry were monitored continuously in all patients. All patients received 0.2 mg/kg IV bolus loading dose of midazolam followed by a continuous infusion starting at  $0.4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . Duration of infusion ranged from 37 to 194 hours. Sedation was judged adequate by the nursing staff and the physician team in doses ranging from 0.1 to  $1.2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . The average infusion rates ranged from 0.387 to  $0.631 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . There were no complications.

### Discussion

Our goal was to establish a level of sedation that would allow the children to remain sedated while intubated and mechanically or spontaneously ventilated, as well as during relatively unobtrusive nursing activities. More stimulating events such as suctioning of the endotracheal tube resulted in breakthrough agitation that required increasing the infusion rate of midazolam 50 to 100% approximately 20 minutes before stimulation. None of the patients developed respiratory depression or oversedation, and all infusions were discontinued at the time of

extubation, or shortly afterwards. Tolerance to midazolam was not observed because infusion rates remained relatively constant.

The infusions did not significantly alter blood pressure or heart rate. Midazolam infusion was not believed to prolong the duration of intubation or weaning from the ventilator in any patient. The nursing staff was uniformly enthusiastic about the degree and control of sedation obtained. Serum midazolam levels were not obtained because previous studies have demonstrated that serum midazolam levels do not correlate well with clinical sedation (10,11).

The benefits of continuous midazolam infusion include easy titration and maintenance of steady state sedation, resulting in decreased adrenergic response to stress. Good anxiolysis, anterograde amnesia, and anticonvulsant properties have also been attributed to midazolam. With therapeutic doses, there is cardiovascular stability (12) with minimal respiratory depression (13). Adrenal cortical depression with prolonged infusion has not been demonstrated (8). In the neurointensive care setting, midazolam may have advantages in that it decreases both cerebral blood flow and cerebral metabolic oxygen consumption in dogs (14). Midazolam has a rapid onset of action and, in the absence of liver disease, cumulation does not occur (15-17). Midazolam is void of significant pharmacologically active metabolites when given intravenously, and has a relatively short elimination half-life of 1.5 to 3.5 hours (5). The incidence of thrombophlebitis related to midazolam is low (18,19), and was not observed in any of our patients.

It should be noted that 1% benzyl alcohol is a preservative in midazolam. Gasping baby syndrome is a fatal consequence of benzyl alcohol poisoning in low birth-weight premature infants (20,21). This syn-

drome was described when premature infants in neonatal intensive care units developed multiple organ system failure unrelated to underlying illnesses. These infants had received  $\geq 98 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$  of benzyl alcohol found in bacteriostatic water used to reconstitute medications and bacteriostatic normal saline used to flush catheters. The premature infant's liver has a reduced ability to detoxify benzyl alcohol and these babies were receiving on a daily basis, 20 to 50 times the maximum safe dose of benzyl alcohol. Should continuous midazolam infusion be used in a 1-kg infant, 49 mg/day of midazolam would have to be administered to accumulate toxic levels of benzyl alcohol. This dose would be 24 times the therapeutic dose we observed in our youngest patient.

In conclusion, we found the continuous infusion of midazolam to be useful for sedation of both ventilated and nonventilated pediatric intensive care unit patients. A loading dose of 0.2 mg/kg followed by continuous infusion at  $0.4 \mu\text{g}\cdot\text{kg}^{-1}$  is a reasonable starting point from which a desired level of sedation can be titrated.

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## Two Instances of Seizure-Like Activity in the Same Patient Associated with Two Different Narcotics

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**Key Words:** COMPLICATIONS—seizures.  
ANALGESICS—fentanyl, sufentanil

Seizure-like activity associated with narcotics has been previously reported (1-4). We recently observed a patient who twice had seizure-like activity, first after sufentanil and subsequently after fentanyl. During the latter episode, EEG recording revealed no unusual central nervous system activity.

### Case Report

A 71-year-old, 80-kg man was scheduled to undergo coronary artery bypass grafting. Past medical history included angina for 20 years, until quite recently relieved with nifedipine, metoprolol and transdermal nitroglycerine; and a stroke 14 years ago, resulting in transient left hemiparesis but no long-term deficit. A few weeks before admission, the patient's angina became refractory to medical therapy.

Immediately after cardiac catheterization, which revealed severe coronary artery disease, he required left ventricular assistance with an intraaortic balloon pump. The patient was brought to the operating room without having received premedication. Immediately before operation his pulmonary and systemic arterial pressures were within normal limits. Cardiac output was 7 L/min. He was given 100% oxygen by anesthesia mask and, after vecuronium 2 mg IV, anesthesia was induced with IV sufentanil 150  $\mu$ g, injected slowly until the patient became apneic and unresponsive to a light tap on the shoulder and a verbal command to breathe. Positive pressure ventilation was then instituted and an additional 8 mg vecuronium given.

Within 10 seconds after the vecuronium injection, the patient's left hand became tremulous. His entire left arm then began to tremble, followed immediately by his left foot and then by trembling of all four limbs. This activity progressed within seconds to a grand-mal seizure with tonic-clonic movements of all extremities. Pulse and blood pressure remained stable within the normal range during the seizure episode. Midazolam 2 mg IV was given. The seizure activity ceased and within another 60 seconds complete muscle relaxation ensued as the vecuronium took full effect. The trachea was then intubated and surgery was postponed.

Neurologic evaluation over the next 3 days was positive only for an old, healed left sided cerebral infarct seen on CAT scan. Once again the patient was brought to the operating room. This time a compressed spectral array EEG (Neurotrac) apparatus was applied. The reference electrode was placed in the middle of the forehead, close to the hairline. Two positive electrodes were placed approximately 2 cm from the reference electrode on either side of the forehead, and one negative electrode was positioned behind each ear on the mastoid processes. This arrangement of electrodes was chosen to allow independent but simultaneous monitoring of both cerebral hemispheres. The apparatus was set to display both raw EEG and the compressed spectral edge.

The patient was premedicated with lorazepam 1 mg PO and morphine sulphate 5 mg IM and brought to the operating room 1 hour later. Again, the patient was given 100% oxygen by mask, followed by vecuronium 2 mg IV. Fentanyl 500 mg IV was slowly injected until, as before, the patient became apneic and unresponsive to a verbal command to breathe and a light tap on the shoulder. Vecuronium 8 mg IV was then given. This time, the patient's right hand initially became tremulous, and again, the patient suffered a grand-mal seizure. However, the EEG did not reveal cerebral seizure activity. Again, pulse and blood pressure remained stable during the seizure

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episode. The operation was performed without further incident.

## Discussion

The literature contains a number of animal studies documenting seizures after administration of fentanyl (5,6). The doses required to cause this reaction range from 20  $\mu\text{g/kg}$  or greater in the cat, to considerably higher dosages in the rat and dog. There have also been a number of case reports documenting seizure-like activity in patients given fentanyl (1,2) and sufentanil (3,4). This is, as far as we are aware, the first observed case of a single patient having such a reaction to both these narcotics. This type of reaction in humans has been associated with relatively low dosages of narcotics—on the order of 6.5  $\mu\text{g/kg}$  fentanyl and 0.7  $\mu\text{g/kg}$  sufentanil. In only one previous report was EEG being monitored during seizure activity associated with fentanyl (7) and, in this instance, as in the present case, the EEG did not show any abnormal central nervous system activity.

Our patient did have a history of a prior cerebrovascular accident (CVA), and the CAT scan after his first episode of seizure-like activity indicated the presence of an old left-sided cerebral infarct. However, our patient had no previous history of seizures and no neurologic deficit after his CVA. The seizure-like activity seen during the anesthetic induction with sufentanil began on the patient's left side, which would not be consistent with a seizure focus in the left cerebral hemisphere. The seizure-like activity during the anesthetic induction with fentanyl began with a tremor of the right hand, but the EEG showed no seizure activity.

The EEG apparatus we used calculates power values from 0 to 63.5 Hz in half-Hz increments and displays in the range of 1 to 30 Hz. The gain is set to detect an amplitude of up to 80  $\mu\text{v}$ . These sensitivities should be sufficient to detect seizure activity associated with a grand-mal seizure.

Considering the number of reported cases of such seizure-like activity in association with fentanyl and sufentanil, and considering that our patient had this

reaction to both these narcotics, an idiosyncratic mechanism for such a reaction would seem to be ruled out. Scott and Sarnquist (7) offer two possible explanations for such events in the absence of seizure activity on EEG. One is that this represents an exaggerated form of narcotic-induced muscle rigidity. This can be ruled out by our own observations. In both instances our patient received a "pre-curarizing" dose of 2 mg vecuronium and full paralyzing doses of the muscle relaxant immediately before the onset of his seizure. Vecuronium 2 mg should be sufficient to prevent the muscle rigidity that is occasionally associated with narcotics and, indeed, in both instances the patient could be easily ventilated by mask, with no evidence of muscle rigidity. It is, of course, impossible to know how long this patient's seizures might have lasted without the full paralyzing effects of the additional 8 mg vecuronium. The second possibility suggested by Scott and Sarnquist is that this reaction is a form of myoclonus secondary to narcotic-induced depression of inhibitory neurons. Our case report suggests that this may well be true, and that the administration of narcotics may be associated, in a reproducible fashion, with myoclonic activity.

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## Acute Postoperative Delirium and Extrapyrarnidal Signs in a Previously Healthy Parturient

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**Key Words:** COMPLICATIONS—delirium. ANESTHESIA—obstetric. ANALGESIA—fentanyl plus droperidol.

Postoperative delirium is a not uncommon complication of anesthetic practice (1). Its etiology can be multifactorial and is often related to physiologic and pharmacologic alterations occurring in the immediate perioperative period. The postpartum period is the most common time for mental disturbances to occur among women (2). We report an unusual case of acute, profound delirium with associated extrapyramidal signs in a previously healthy woman after an uneventful cesarean section.

### Case Report

The patient was a 35-year-old, previously healthy woman with a full-term intrauterine pregnancy presenting for an elective cesarean section after an unremarkable prenatal course. Past medical history was notable for a previous cesarean section under continuous epidural anesthesia. During this procedure the patient experienced significant pain and thus was extremely apprehensive about her current anesthesia. There was no history of substance abuse but family history was positive for schizophrenia in a brother. Preoperative physical examination and laboratory values were normal for a pregnant woman with term gestation.

Anesthesia was begun at 0635 hours. After placement of an IV catheter and the usual monitors, the patient was put in the left lateral position and an epidural puncture was made between the third and fourth lumbar vertebrae using the "loss of resistance"

technique. A catheter was easily inserted and a test dose of 3 ml 1% lidocaine without epinephrine was injected without development of spinal anesthesia. Injection of 20 ml of 2% lidocaine with epinephrine was then performed and decreased sensation up to the level of the fourth thoracic dermatome resulted. After the surgical incision (at 0710 hours), the patient was comfortable with a blood pressure of 110/52 mm Hg and a pulse of 70 beats/min. A healthy baby girl (Apgar scores of 8 and 8) was delivered at 0730 hours. Fentanyl 100  $\mu$ g was then administered intravenously. Several minutes later, the patient complained of nausea and began retching. Bradycardia (to 50 beats/min) occurred without change in blood pressure. Atropine 0.4 mg IV brought the pulse back to 100 beats/min. However, the patient continued to complain of nausea and so at 0805 hours, just as surgery was ending, she was given droperidol 1.25 mg IV. The estimated blood loss was 1000 ml and the total amount of Lactated Ringer's solution administered intraoperatively was 3000 ml.

On arrival to the recovery room (at 0810 hours) the patient was awake but complained of feeling faint. The blood pressure was 78/40 mm Hg and the heart rate was 62 beats/min. Vital signs became normal after an IV fluid bolus and a single dose of metaraminol (1 mg IV). Over the next 2 hours, the patient regained full sensation and motor control of her trunk and lower extremities. She was noted to be lucid, appropriately oriented, and hemodynamically stable. At 0830 hours, the patient complained of incisional pain and was given 100  $\mu$ g fentanyl epidurally (mixed in 8 ml sterile preservative-free saline) and an epidural fentanyl infusion was started at a rate of 50  $\mu$ g/hr. She was transferred to a ward room at 1030 hours.

The anesthesiologist was called by the ward nurse at 1130 hours because the patient had become increasingly lethargic, confused, and tremulous. On arrival, the anesthesiologist found the patient to be unresponsive with marked coarse spontaneous myoclonic jerking movements of her face and all four

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extremities. Vital signs were normal. The epidural fentanyl infusion was stopped and naloxone 0.4 mg IV was administered in divided doses. The patient became slightly less obtunded but was still completely disoriented and failed to follow simple commands. She continuously vocalized meaningful words in a random nonsensical order ("word salad"). The coarse tremor of her face and extremities persisted. A divergent gaze was noted. Arterial blood gas analysis revealed pH 7.33,  $P_{aO_2}$  80 mm Hg, and  $P_{aCO_2}$  46 mm Hg. Sodium was 130 mEq/L, potassium 4.0 mEq/L, serum glucose normal, and hematocrit 26%.

Because of the suspicion that the patient's symptoms were due to iatrogenic drug toxicity, she was given physostigmine (1 mg IV twice) with glycopyrrolate (0.4 mg IV). Within minutes she became oriented and able to respond appropriately to commands but the tremulousness of her extremities failed to resolve. The patient was completely amnesic to the events of the entire morning and thought she was still pregnant. She denied any pain on repeated questioning. Over the next 30 minutes, the level of consciousness deteriorated to its previous unresponsive state. A repetition of the physostigmine (2 mg IV) along with naloxone (0.4 mg IV) produced a similar, transient improvement in her cognitive state.

A computerized tomographic scan of her head was normal, as was a urine toxicology screen. Over the next several hours, her level of consciousness improved although she remained delirious. A neurologist, examining the patient 8 hours postoperatively (at 1600 hours), found her to be lethargic but comfortable. The patient would briefly follow simple commands but then would begin "babbling" and become uncooperative. The pupils were 4 mm and reactive to light. There was a pronounced resting tremor of the tongue, hands, and feet, which became worse with intention. A significant flexion-extension tremor of the neck and "jumpy" eye movements were also noted. There was a purposeful and symmetrical withdrawal of all four extremities in response to painful stimulation. The upper extremity reflexes were hyperactive while those in the lower extremities were hypoactive. The neurologist's working diagnosis was a drug-induced psychosis.

The patient was transferred to an intensive care unit for closer observation and supportive care. Blood pressure and HR remained in the normal range although she was noted to have a low-grade fever (37.7°C). Urine output remained adequate. Because of the persistent tremors, diphenhydramine 30 mg IV was administered empirically without immediate im-

provement. Nevertheless, her symptoms slowly began to resolve.

Neurologic examination 23 hours postoperatively found the patient to be alert but completely amnesic for the previous day's events. She was oriented to person and place but not to time. She could not correctly name the current President of the United States and had difficulty with serial 7s. She was unable to remember three objects for two minutes. Her speech was fluent but tangential and contained neologistic errors. While the neck tremor had resolved and the tremor of the lower extremities had improved, she still had a pronounced intention tremor of the tongue and upper extremities. Sensation, motor strength, cerebellar, and cranial nerve function were intact. Babinski reflexes were bilaterally positive.

By the evening of the second postoperative day, 36 hours after the completion of surgery, the patient was essentially normal. She was discharged on postoperative day 7 with a clinical diagnosis of "acute postoperative encephalopathy with extrapyramidal symptoms" and has experienced no further problems.

A chemical analysis of the intravenous bag containing the fentanyl for epidural infusion revealed an appropriate fentanyl concentration and no detectable contaminants.

## Discussion

This report describes an impressive acute delirium with associated profound dyskinesia that developed in a previously healthy parturient 3 hours after the completion of an epidural anesthetic for an elective cesarean section. Transient reversal of the patient's cognitive symptoms was produced by physostigmine but by neither naloxone or diphenhydramine. The symptoms resolved spontaneously after 36 hours.

The differential diagnosis of postoperative delirium is extensive (Table 1). Major elements of this list include: drug reactions; changes in central nervous system metabolism, perfusion, or oxygenation; exacerbation of a premorbid neurologic or psychiatric disturbance; and psychological stresses unique to the surgical experience. The current case exemplifies the additional complexities associated with the clinical assessment of delirium in the postpartum patient.

## Drug Reactions

Of the drugs given this patient, fentanyl, droperidol, and atropine are all capable of producing delirium.

Table 1. Factors in Postoperative Delirium

I. Physiological factors
A. Factors that principally decrease cerebral oxygen delivery
Decreased cardiac output (hypotension, arrhythmias, hypovolemia)
Cerebrovascular insufficiency (occlusive or embolic)
Hypoxemia or anemia
Hyperviscosity or coagulopathy
Increased intracranial pressure
B. Factors that principally increase cerebral oxygen demand
Stress
Hyperpyrexia
Infection
Hyperthyroidism
Hypercarbia or acidosis
Seizures
C. Factors that alter cerebral metabolism or function
Malignant hypertension
Metabolic factors
Hepatic or renal dysfunction
Ionic imbalances (e.g., glucose, sodium, calcium, potassium)
Endocrine imbalances (hypothyroid, adrenal insufficiency)
Drug toxicity
Heavy metals, thiamine, or carbon monoxide
Ketamine, neuroleptics, opiates, sedatives, anticholinergics, hallucinogens
Withdrawal from alcohol, barbiturates, hallucinogens, opiates, benzodiazepines
Neuroleptic malignant syndrome
Allergic or idiopathic reaction to administered drugs
CNS disease processes
Dementia or chronic organic brain syndrome, Parkinson's, multiple sclerosis
Encephalitis (bacterial, viral, fungal)
Cerebral contusion or injury
II. Environmental and psychosocial factors
A. Factors that principally affect normal sensory integration
Sleep deprivation
Impaired ability to communicate
Sensory deprivation, monotony or physical isolation
Impaired mobility
B. Factors that can increase fear and anxiety
Pain and discomfort
Incisional pain
Gastric or bladder distention
Environmental factors including noise, frightening activities, etc.
Bad previous experience in a similar setting
Surgical procedure
Position
Extremes of age
Preoperative vocational or retirement-related problems
Feelings of dependence, hopelessness, and loss of dignity
C. Psychiatric factors
Underlying psychotic or neurotic (especially paranoid) disorder
Endogenous depression
Postpartum psychosis
Conversion reaction
Inadequate preoperative defenses and coping mechanisms
Morbid or pessimistic expectations
Body image distortion

However, with all three of these agents, drug-induced delirium typically follows larger doses or more prolonged exposures. High dose opiates, for example, can produce CNS excitatory effects that are often accompanied or followed by seizures. These effects typically occur at doses far in excess of those necessary for adequate analgesia and are usually naloxone-reversible (3). There are no previous reports of excitation associated with epidural fentanyl. Changes in endogenous opiate activity has been implicated in the etiology of some psychotic states (4) and specifically in postpartum psychosis (5). When fentanyl is administered as a premedication in a fixed combination with droperidol (Innovar), a 1-4% incidence of refusal to undergo surgery has been reported (6). However, it is unclear whether the psychotropic effects of Innovar are due solely to droperidol or if the fentanyl also plays a role. The relatively low dose of fentanyl administered and, particularly, the lack of response to naloxone make it relatively unlikely that the symptoms exhibited by this patient were due to acute opiate toxicity.

A frequent adverse reaction to acute administration of neuroleptic drugs is dyskinesia, including torticollis, grimacing, and other involuntary muscle movements, occurring in 12% of all patients. In these reactions, consciousness is typically not impaired (7); and symptoms are usually rapidly and completely reversed after the administration of agents with anticholinergic activity (8), including diphenhydramine (9). In contrast, cholinergic agonists such as physostigmine usually exacerbate the symptoms. Although the spectrum of extrapyramidal symptoms exhibited by this patient may be consistent with a neuroleptic-induced acute dyskinesia, the marked impairment of consciousness and the lack of therapeutic response to diphenhydramine both argue against such an explanation for this presentation.

The "neuroleptic malignant syndrome" (NMS) is a less frequent adverse reaction to neuroleptic agents (occurring in 2.4% of all patients) (10). The cardinal symptoms of NMS include muscle rigidity, extrapyramidal signs, hyperthermia, autonomic dysfunction, and altered consciousness, although considerable variation in the presentation has been described (11). Although most cases of NMS occur in patients receiving chronic neuroleptic treatment for psychiatric illness (11), it has been reported as a postoperative complication of higher doses of neuroleptics in a patient without a prior psychiatric history (12). There have been reports of successful treatment of NMS with dantrolene sodium (13) and bromocriptine (14) but not physostigmine. Nonetheless, the diagnosis of NMS must be entertained in the setting of the acute



onset of extrapyramidal symptoms, diminished mental status, hypotension, and fever in conjunction with neuroleptic administration.

Neuroleptics have also been implicated in postoperative confusional states (15) that occasionally follow higher doses of droperidol (5 mg IV) and can be prolonged—with some effects measurable as late as the fourth postoperative day (16). Interestingly, impaired mental status after droperidol is often ameliorated by physostigmine (17–19). In the present case, an acute neuroleptic-induced confusional state might be intensified by CNS anticholinergic effects produced by the intraoperative administration of atropine (20,21). Central nervous system symptoms of anticholinergic toxicity frequently include delirium, psychotic behavior, and motor disturbances (22). As with our patient, these symptoms typically resolve rapidly after the administration of physostigmine (23). Because of physostigmine's rapid metabolism, in contrast to the protracted time course of atropine toxicity (often lasting >48 hours), repeated doses of physostigmine are usually required (22). Physostigmine also appears to have nonspecific CNS "activating" properties that may reverse the effects of general anesthetics (24). For instance, there has been a report of physostigmine reversing postoperative somnolence and disorientation associated with the intraoperative administration of Innovar, a fixed-dose combination of fentanyl and droperidol (17).

### *Physiological Factors*

Any factor impairing the delivery of an adequate amount of oxygen to brain cells relative to their metabolic needs affects cerebral function and could potentially result in delirium. Hypotension and hypoxia may, therefore, cause postoperative delirium. Although there was a transient episode of hypotension on arrival to the recovery room in this patient, neither its duration nor its magnitude were sufficient to produce prolonged CNS effects. Likewise, there was nothing to suggest a decrease in cerebral oxygen delivery (oxygen saturation as measured by pulse oximetry remained normal both intraoperatively and in the recovery room), an increase in cerebral oxygen demand, or alterations in cerebral metabolism (see Table 1). Toxic or metabolic causes of the patient's symptoms seem unlikely in view of her previously healthy condition.

Thromboembolism is not a rare occurrence in parturients and could result in a delirium. However, the delirium associated with thromboembolism is probably due to hypoxemia (25). Amniotic fluid embolism

might present with changes in mental status, pulmonary hypertension, cyanosis, or acute heart failure. Usually there is an accompanying coagulopathy (26). The fact that this patient had a self-limited delirium along with a profound dystonia in the absence of cardiopulmonary or other systemic signs strongly suggests that physiologic causes can be excluded.

### *Psychiatric Causes*

Altered mental status in the postoperative patient can certainly be associated with a premorbid psychiatric illness. This is particularly true for organic psychosis, schizophrenia, and bipolar affective disorders. Such patients are often exquisitely sensitive to CNS drug effects and the stress or disorientation associated with the postoperative or postpartum state (2). There is no indication of a premorbid psychiatric illness in the present patient, although there is a positive family history of schizophrenia in a sibling. A psychiatric syndrome unique to the postpartum patient, puerperal psychosis, is characterized by confusion, cognitive disorganization, and manic symptoms including euphoria and hyperactivity within the first postpartum month (27,28). The rapid onset and complete resolution of the extrapyramidal symptoms in this patient is not a typical presentation for postpartum psychosis.

In summary, the present clinical report documents an unusual instance of acute florid postoperative delirium with associated extrapyramidal signs in a previously healthy parturient. The potential causes of either postoperative or postpartum delirium are numerous and in many cases a multifactorial etiology can be implicated. In the present situation, it appears that atropine, droperidol, and perhaps also fentanyl, administered during the anesthetic, were responsible for the patient's delirium. This parturient may have been particularly sensitive to the CNS side effects of commonly administered anesthetic drugs. Small doses of these otherwise safe and effective drugs may, in combination, produce significant postoperative psychomotor disturbances in selected patients, especially in clinical situations in which other factors predispose to postoperative delirium.

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## Letters to the Editor

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### Modular Intravenous Transport System

To the Editor:

Transport of sick patients to and from the intensive care unit is often a cumbersome process that requires pushing numerous poles and infusion pumps behind the patient's bed. We have spent 3 years designing and testing various types of racks that could be fitted to the bed, allowing patient movement without the necessity of trailing poles. The design we present here has been our most effective and least expensive.

The modular rack system has several components made of chrome-plated stainless steel as shown in Figure 1. The

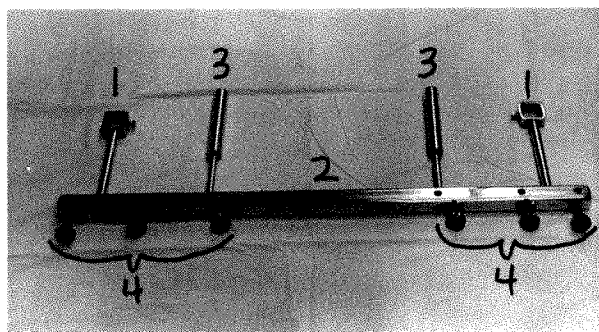


Figure 1. Components of the Intravenous Transport System: 1) vertical support rod; 2) cross bar; 3) adaptor for IVAC infusion pump pole; 4) knob-head bolts.

vertical support rods fit into the holes normally provided in the bed for intravenous poles. The cross bar slides through the square openings at the top of the support rods and is clamped in place by bolts. Each cross bar contains six half-inch holes that can support intravenous poles while still allowing access to the patient. The poles are secured by hand-tightened knob-head bolts. Most commercially available intravenous poles can be accommodated. Some may require minor modification. We have also designed an adaptor that can be used to mount transducers or the entire upper portion of an IVAC infusion pump pole. Figure 2 shows such an assembled system.

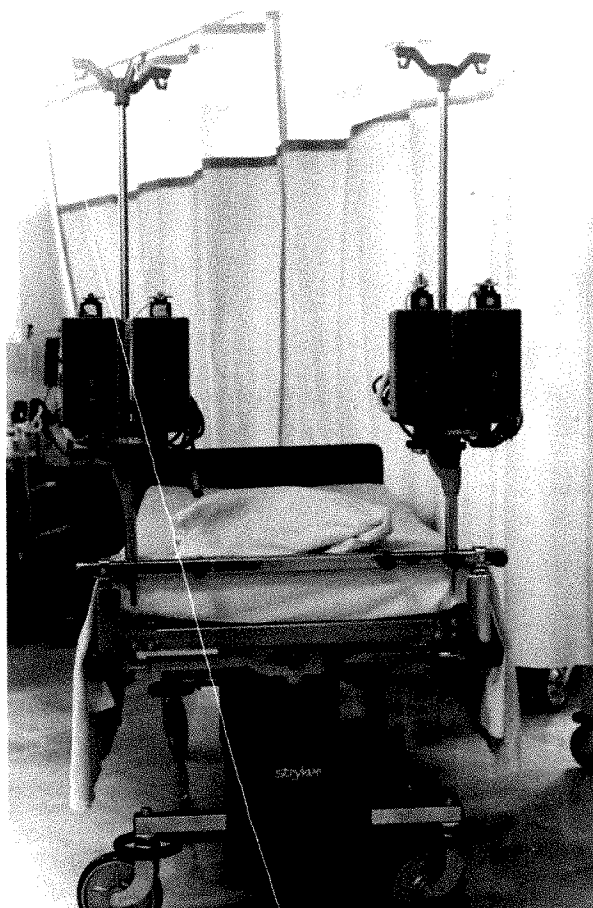


Figure 2. Bed-mounted transport system.

We have found that this system cuts down the time needed to mobilize and transport patients, while resulting in fewer line tangles at the destination point. This is especially useful during emergencies requiring rapid movement from the intensive care unit to the operating room.

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## Preventing Kinking of Small Endotracheal Tubes

To the Editor:

We read with interest the recent letter by Yamashita and Motokawa (1) concerning the potential kinking of 2.5-mm ID endotracheal tubes used in premature babies undergoing neurosurgery, ophthalmic surgery, oral surgery, and ENT surgery. These authors stated that such kinking may be prevented by cutting a disposable 3.5-mm ID Portex tube 4 cm from the distal end and inserting the 2.5-mm ID Portex tube (3.4-mm outer diameter) through this 3.5-mm ID tube, leaving the distal 4 cm of the 2.5-mm ID tube uncovered. We would offer several comments on their communication.

1. Multiple attempts by ourselves and our colleagues to slide currently available 2.5-mm ID (3.4-mm outer diameter) Portex tubes through 3.5-mm ID Portex tubes were usually unsuccessful and the use of lubrication did not improve our results.
2. The standard 2.5-mm ID Portex tube is 15 cm in length, whereas 3.5-mm tube is 19.5 cm. Shortening the 3.5-mm tube by 3 cm, as described by Yamashita and Motokawa (1), would result in similar lengths for both tubes! These technical difficulties may be resolved by employing a 4.0-mm ID, 23-cm length outer tube that has been shortened by 8.5 cm.
3. We nevertheless remain concerned over the possibility of direct vocal cord trauma being caused by the outer tube. This may occur with distal sliding of the outer "endopharyngeal" tube or, more commonly, by distal displacement of both tubes during head repositioning. The latter is a not infrequent occurrence during anesthesia for procedures around the head and neck (2,3).

Recognizing that the proximal (connector) end of the 2.5-mm ID endotracheal tube is the most common site for kinking, we propose the following alternative solution to this problem. The standard 2.5-mm plastic adapter is replaced by a 3.0-mm metal curved connector (Dupaco, Oceanside, CA; Foregger, Langhorne, PA) and the proximal part of the 2.5-mm tube is wrapped with a 3-4 cm length of tubing (e.g., suction catheter, oxygen or endotracheal tubing), which is 1.0 mm greater in ID and has been split longitudinally down one side to facilitate placement around the smaller tube. We have used this technique successfully in the care of small infants, both in the OR and ICU, and have found it to reliably prevent kinking of small size (2.5 to 3.5-mm ID) endotracheal tubes while at the same time reducing the risk of trauma to the vocal cords.

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## Epidermolysis Bullosa and Porphyrria

To the Editor:

It is important that articles such as that by Broster et al. (1) continue to appear in the anesthetic literature because this allows for the accumulation of data relating to anesthesia in rare disorders. However, it is important that any information presented should be both current and accurate. We wish, therefore, to comment on the statement in Broster's article that porphyria has an increased incidence in patients with epidermolysis bullosa (EB).

It is true that many authors have suggested that an association between EB and porphyria exists, but this does not appear to have been substantiated. References in the anesthetic literature to the association can be traced to two textbooks of dermatology published in the 1960s (2,3). Andrews and Domonkos simply write, in a section about EB, that "porphyria may be present" (2). Marshall (3) goes so far as to question the very existence of what he calls the nonporphyric type of epidermolysis bullosa, also stating that "epidermolysis bullosa porphyrica" is an alternative term for porphyria cutanea tarda (PCT). Even the statement by Katz et al. (4,5) that EB and porphyria are associated, which has been further quoted in recent years by other authors, is not substantiated.

In the past there has obviously been considerable diagnostic confusion between EB and porphyria. Indeed, porphyrin excretion may be within normal limits in patients with porphyria for long periods, and this has been one area of confusion. The skin lesions of EB and PCT may be identical, PCT being the type of porphyria most likely to be confused with EB. However, nowadays they can be distinguished on the basis of histopathologic, immunofluorescence, and porphyrin studies (6).

Thus, we contend that today there is no evidence to substantiate the association between EB and porphyria. Of course, porphyria should be included in the differential diagnosis of EB and other blistering diseases, and porphyrin studies should be performed in patients with undiagnosed bullous disorders. However, it is probably an unnecessary precaution to withhold barbiturates from patients with EB, particularly because these and other drugs likely to induce hepatic porphyrias appear to be safe in patients with PCT (6,7).

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## Demonstrating Safety of Subarachnoid Calcitonin: Patients or Animals?

To the Editor:

Although Miralles et al. (1) demonstrate convincingly that subarachnoid calcitonin is an effective analgesic, I disagree with their conclusion that "demonstration of its safety requires the study of a larger number of patients." The authors do not mention animal toxicology of subarachnoid calcitonin. Current Medline files contain only two references to animal safety testing of subarachnoid calcitonin, and both describe toxicity. In rats, subarachnoid calcitonin reversibly inhibits motor coordination (2), whereas in dogs and baboons, subarachnoid calcitonin produces respiratory distress leading to a moribund condition (3). There are no subsequent reports examining the etiology of these effects, including the possibility that they are due to preservatives in the original calcitonin solutions. Likewise, there are no references to neurotoxicity studies of subarachnoid calcitonin in current Medline files. One could argue that subarachnoid calcitonin is probably safe, because calcitonin is normally present in small amounts in CSF. However, the effects of high local concentrations of calcitonin on the spinal cord are unknown, and another hormone, angiotensin, produces severe vasoconstriction when applied locally to pial vessels (4). Likewise, the absence of toxicity observed after subarachnoid calcitonin in a small number of patients (1,5-7) is not an effective argument for further clinical trials in the face of this preliminary animal work. I conclude that demonstrating safety of subarachnoid calcitonin (and many of the opiate and nonopiate drugs being injected spinally before animal testing) requires first the study of a larger number of animals, not humans. At least, effects on blood pressure, heart rate, arterial blood gas tensions, animal behavior, and spinal cord histology and blood flow should be examined.

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## Subarachnoid Lidocaine and Calcitonin for Postoperative Analgesia

To the Editor:

The study of Miralles et al. (1) reported postoperative analgesia to be greater in patients given subarachnoid injections of lidocaine (LI) and salmon calcitonin (sCT) than that in patient given only subarachnoid LI. There are, however, data that speak against the use of sCT as an analgesic agent. For example, the spinal cord has but few binding sites for sCT (2,3). Also, in spite of numerous reports of the analgesic effect of centrally administered sCT in animals (4), sCT injected intrathecally in rats has no analgesic effect, but does have a long-lasting, reversible blocking action on motor function (4).

The analgesic effect of subarachnoid sCT in cancer patients (5) is probably due to nonspecific effects (4). All in all, sCT does not fulfill the conditions of a real analgesic agent (6). Also, toxic effects of subarachnoid sCT have been reported (7). Finally, in the study of Miralles et al., sCT was administered together with LI. Small doses of systemically administered LI have, however, pronounced transsynaptic effects on spinal cord activity evoked by unmyelinated afferents (8), the majority of which are nociceptors. Epidural LI can, therefore, be expected to have, aside from its local anesthetic effect, a depressive function on the synaptic efficacy of nociceptive inputs. The possibility of an interaction between LI and sCT has not been tested and may be involved in the effects observed by Miralles et al.

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## The Effect of Age on Plasma Clearance of Epidural Lidocaine and Bupivacaine

To the Editor:

Veering et al. (1) recently reported that plasma clearance of epidural bupivacaine was negatively correlated ( $r = 0.57$ ;  $P = 0.001$ ) to the age of the patients. It may be of interest to these authors and other readers that we reported similar results for epidural lidocaine last year. The correlation coefficient for plasma clearance of lidocaine and age was  $-0.41$  ( $P < 0.01$ ) in 50 male patients ranging in age from 22 to 78 years (2).

Although the clearance of both lidocaine and bupivacaine declines with age, the mechanism may be different for the two drugs. Lidocaine is highly extracted by the liver (extraction ratio  $> 0.9$ ); clearance is thus substantially dependent on liver blood flow (3). Because liver blood flow normally declines with age (4), lidocaine clearance is expected to decline as well. On the other hand, bupivacaine clearance is relatively insensitive to liver blood flow (extraction ratio approximately 0.2). Therefore a reduction in bupivacaine clearance may reflect a reduction in the activity of bupivacaine metabolizing hepatic enzymes (5). That hepatic drug metabolism declines with age is well established in animals (6). In humans, liver mass is con-

stant until middle age, at which time it begins a progressive decline (7). However, the extent to which human microsomal enzyme activity is affected by aging is unclear (8). Antipyrine is a model compound for the study of hepatic drug metabolism, because its clearance is limited by the activity of hepatic enzymes. Vestal et al. (9) reported a correlation between age and antipyrine clearance of only  $-0.25$  ( $P < 0.001$ ). Thus, interindividual differences in metabolism due to a variety of genetic and environmental factors were of relatively greater importance than was age.

Finally, although there is a significant correlation between age and clearance of both lidocaine and bupivacaine, the variation in clearance at any particular age is quite large. For example, some patients older than 70 years of age have a lidocaine clearance greater than some patients younger than 30 years of age. This was found in the recent study of bupivacaine clearance as well.

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## Book Reviews

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### Manual of Anesthesia for Emergency Surgery

Judith Donegan, ed. New York: Churchill Livingstone, 1987, 403 pp, \$29.00.

One of the most exciting attractions of the specialty of Anesthesiology is the sudden presentation of a patient for emergency surgery. This provides the anesthesiologist that unique situation in which he or she draws on past experience and knowledge to minimize the risks that the patient must face during this ordeal.

The editor states precisely in the preface that this is an outline presented in manual form of quick and accessible information needed to anesthetize patients for practically all types of emergency surgery. The editor does not indicate which reader would benefit from this manual, but certainly residents, fellows, CRNAs, and practicing anesthesiologists who want to quickly refresh their memory would find the information extremely useful.

The list of authors who have written many of the specialty chapters are well-known in anesthesiology and though much of their information is extremely valuable, it is mainly reproductions of previous chapters they have written in other textbooks. The author has, however, used this as a very attractive drawing card and has assembled the approaches many of these experts utilize in anesthetizing emergency patients.

The chapters are all organized in a cookbook, easy to read style with sections on 1) patient preoperative evaluation and preparation, 2) anesthetic management and, 3) postoperative care if there are specific problems that relate to this period. There is an adequate list of references and suggested readings at the end of each chapter.

Practically every common emergency procedure is described in specific sections including interesting chapters on 1) alcohol abuse, 2) cardiopulmonary resuscitation, 3) shock and, 4) sepsis. The chapters provide the reader with a very practical approach on how to manage all types of emergencies with enough preoperative information and workup that apply to each of the specialty areas. The style is one that can be read quickly so that one can come away with the salient features of specific management. The editor's goal is the overall reduction in perioperative morbidity and mortality associated with emergency care of surgical patients. If enough residents, CRNAs and anesthesiologists review the material before proceeding with their anesthetic management, this may in fact be borne out.

There should be fewer omissions or commissions of medical management under these circumstances.

One might say there might be no need for such a book because all this material is readily available in many other textbooks. However, the author has now assembled all this information in one area that is very portable and extremely accessible. Certainly in large and busy teaching centers where residents, CRNAs and fellows are training, a readily portable manual with good information may decrease the incidence of complications that are associated with emergency surgery.

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### The International Textbook of Cardiology

T.O.Cheng, ed. New York: Pergamon Press, 1986, 1297 pp, \$87.50.

The physician today who strives to be well-read is blessed or handicapped, depending on one's viewpoint, with a wide choice of textbooks on the same subject. Perhaps partly as an effort to distinguish this book from among the ranks of the comprehensive cardiology texts available, the editor emphasizes the multinational roster of contributors and his goal of underlining international differences. In spite of the title, this book is mainly a Sino-American endeavor, as only 18 of more than 100 contributors are based outside the United States or China. There is a distinct tendency toward equating "international" with "Chinese."

Few anesthesiologists as mortals would likely read such a volume from cover to cover. What interest then can the anesthesiologist possibly have in this book? This reviewer believes there are three possibilities: 1) the book as a complete reference work to own; 2) the book as a sourcebook on "exotic" cardiovascular disease and; 3) the book as a colloquium of cross-cultural or cross-national perspectives for the informed physician.

The 83 chapters of this book cover a wide range of subjects, including the standard ones appropriate in a comprehensive textbook of cardiology. Several chapters are distinguished by their respective pioneer-authors: Chavoz on thrombolysis, Barlow on mitral valve prolapse, Bjork on

valvular surgery, and Swan on myocardial infarction. There is a fairly large section dealing with invasive intervention such as the intraaortic balloon, the left ventricular assist device, and the artificial heart. The chapter on aortic surgery is authoritative and beautifully illustrated. Together these chapters form a manageable update for those whose practice does not routinely involve cardiovascular surgery. Other advances and "frontier" subjects of cardiovascular research, such as lasers, rapid computerized tomogram, antibodies, and atrial natriuretic factor are discussed and placed in perspective. The chapter on iatrogenic disease is a useful reminder of medicine's potential to do more harm than good.

As a comprehensive reference, the book falls short in several aspects. One of the weakest areas is in normal, systemic physiology of the cardiovascular system. As an example, there is no discussion of diastolic function. The level of discussion and bibliography varies among the chapters, probably more than would be expected in a book of such intended stature. Although several chapters such as those on electrophysiology, mitral valve prolapse, and infective endocarditis, are thorough and complete reviews with extensive bibliography, others are below this standard. For example, the chapters dealing with rheumatic heart disease, antiarrhythmic drug therapy; inotropic drugs, pediatric congenital heart disease, and surgery of valvular heart disease are notable for the brevity of references, and the content of some of these chapters are more suited as introductory overviews. Some other subjects suffer from obvious omissions. The coronary care unit, which has significantly reduced the mortality of acute myocardial infarct patients, receives no separate mention in the entire textbook, even with the inclusion of a separate chapter on cardiovascular nursing. The content of the latter is more rhetorical than substantive. The discussion on pacing makes no mention of emergency pacing, transthoracic pacing, or pacing via a pulmonary artery catheter. At the other end of the spectrum, one may quibble with the necessity of a separate chapter on anesthesia for cardiac surgery in a general textbook. More useful to improving the understanding between the internist-cardiologist and the anesthesiologist would be a chapter on anesthesia for noncardiac surgery. In spite of the significant advances made in obstetrical anesthesia and data attesting to the role of anesthesia (especially regional anesthesia) in caring for the high risk parturient, this reviewer is disturbed and frustrated by the dated and unflattering, passing reference to anesthesia in the chapter on pregnant cardiac patients.

How useful is this as a sourcebook on "exotic" diseases or approaches? Keshan disease, herbal cardiovascular pharmacology, and acupuncture analgesia are certainly fascinating and unique subjects, although the latter may be a little out of place in a cardiology textbook. Other uncommon disease are not covered with much unusual insight. For example, Kawasaki's syndrome is discussed by a U.S. author in three short paragraphs, and Chagas' disease, a major public health problem in South America, is discussed by an Indian, not an American, author.

How well does this book serve to convey collective viewpoints or comparative opinions from across the nations? It is largely disappointing. Aside from several chapters dealing with epidemiologic issues, there is little internationalism within individual chapters. For example, it would have been very interesting and helpful to the uninitiated if the discussion on herbal pharmacology had been placed in the perspective of "traditional" western cardiovascular pharmacopeia. Other areas amenable to collective international wisdom may include a comparative approach to anesthesia for patients with heart disease (including acupuncture), allocation (or its lack) of resource to cardiac patients, and choice between medical and surgical treatment of heart disease. Ironically, this very textbook exemplifies the problem of provincialism exposed by Chapter 83, "Medical Communication in Cardiology." In a broader sense, this provincialism extends to medicine as a whole, pitted against the other humanities. Indeed, in these times of shrinking resources and rising physician accountability, are we entitled to single-minded advocacy of more cardiac surgery programs in the third world, as suggested by the author of Chapter 75, in the midst of basic public health problems?

In summary, this is an interesting book to browse through for those who are looking for a comprehensive overview on a large number of medical and surgical cardiology topics, including some new advances. Although it has several exceptional chapters, it falls short of standing alone as a complete reference work. The "international" aspect is well-intended but fails to bring much additional insight.

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### Anesthesiology: A Concise Textbook

T. J. DeKornfeld, ed. New York: Elsevier Science Publishing Company, Inc., 1986, 560 pp, \$33.95.

The reviewer apologizes to the editor and authors of this textbook for the delay in its review. More than 18 months have elapsed since the assignment to assess was accepted. In expiation, the task was impossible, partly because this is really several books sharing one cover, and partly because the authors and editor have really not understood and agreed upon either the level of presentation or its likely audience. I began this review by reading the foreword, a trade against those who do not read the foreword. There I found that 1) it is intended for medical students and ab initio anesthesiologists and, 2) a chapter on equipment was omitted by intention. Surely, it was the gadgetry that initially attracted me to the specialty. And although mention of machines and monitors is not vital to the editor's aims, it is like eating a meal without cake or ice cream—pure nutrients, vitamins, and green vegetables. Because



only three of the five sections of the text struck me as valuable, what follows here is a review with mixed feelings.

The first section (7 of 40 chapters) is the best, representing a resource not collectively available anywhere else. Thought-provoking essays by clear thinkers writing concisely cover history, education, ethics, the law, economics, practice patterns, and the care team in the context of current anesthesiology. A laudable review would come from considering these contributions alone. By themselves, they would be worth the price, so all else is a bonus.

The next eight chapters are, I suppose, obligatory topics for a book pointed at medical students. They variously succeed or fail. Theories of anesthesia, admittedly incomplete, are categorized as correlation, neurophysiologic, biochemical or molecular, and our misgivings about each are separately noted. Patient assessment and the preoperative visit are, in my view, different tasks, but herein are combined and presented without a single subheading, illustration, or other break for organization. It came across as heavy stuff to a dozen medical students on whom I tried it out. But when broken into the four steps it identifies, and with headings added, it is perceived as clear and organized. The piece on anesthetic techniques takes the English model of three components instead of the earlier Woodbridge four-component concept of nothria (strange for an American text). It also gives local anesthesia equal billing with regional anesthesia and general anesthesia, which seems to artificially divide the uses of cocaineoids, and to slight general agents. The chapter on pharmacology includes too much review of dynamics and kinetics at a basic level and too little exposition of the special qualities of anesthetic agents and adjuvants: the kinetics of inhalation dosing, for example, are unusual in general pharmacology and paramount in inhalation anesthesia. The chapter on monitoring has detailed, institution-specific, protocols for intravascular access but little to guide one in the use of the data provided. Radial artery cannulation is given twice the space of ECG monitoring as an example of misplaced imperatives. "Computers and Anesthesia" was written as a review for junior high school hackers. Essays on respiratory care and recovery room care are concisely competent. In summary, these eight chapters could well have been provided as mimeographed lecture notes for medical students and left out of the textbook, at no net loss. Half a dozen cheaper books cover these areas better.

Thirteen chapters cover 12 "Anesthesia for . . ." by surgical specialties. I found them useful to give a student, one by one, before spending a day in the ENT room, the orthopaedic room, the urologic suite, etc. Although no one chapter provides everything a student could be told, each has a worthwhile number of cogent points and probably more than a student wants to be told. One can assign a chapter and fully expect a student to read it before arrival in the OR next day.

Similarly, nine chapters provide advice for "The Patient with . . . Disease," covering common patient management problems in systematic fashion: heart disease, pulmonary disease, renal disease, etc. When a student comes back from initial preoperative assessment, he or she can be directed to one or two of these chapters to provide him or her with the anesthesiologist's alternatives and advice for common conditions.

The last section labeled "miscellaneous" borders on the useless; e.g., two and one-half pages on how to read science. The equations and derivations of the penultimate chapter are often just plain wrong at a high school algebraic level.

The subtitle of this volume is "A Concise Textbook." I'll tell you a secret. It got to be concise by taking a big book and removing most of the tables, figures, charts, diagrams, illustrations, as well as the space consumed by liberal use of heading and subheadings which illuminate and enlighten a mass of text. Two of the chapters contain 19 of the less than 30 figures in over 500 pages of text. Many chapters have no illustrations, tables, subheadings, or other breaks. Leafing through the book, the student gets a dull, stolid feeling. I've watched them and nothing seems to grab their attention. Assignments are initially regarded as a chore, re-deemed only by the fact that I didn't require they read the whole thing. On the other hand, fairly senior anesthetists have enjoyed and profited by readings from the first section of the book. Possibly, the real audience is not students and beginning trainees, but practicing anesthesiologists.

Theodore C. Smith, MD  
Professor of Anesthesiology  
Loyola University  
Maywood, IL 60153

#### Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Aldrete JA. *Texto de anestesiología teórico-práctica*. Puerto Rico: Salvat Mexicana de Ediciones, 1986, 918 pp.

Martin JT, ed. *Positioning in Anesthesia and Surgery*. 2nd Ed. Philadelphia: WB Saunders, 1987, 347 pp, \$45.00.

Murphy CH, Murphy MR. *Radiology for Anesthesia and Critical Care*. New York: Churchill Livingstone, 1987, 273 pp, \$50.00.

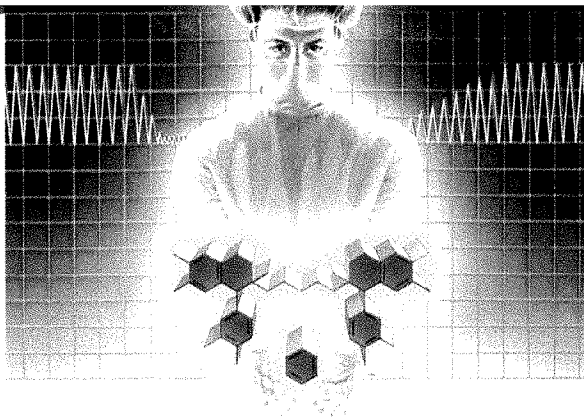
Nunn JF. *Applied Respiratory Physiology*, 3rd Ed. Stoneham, MA: Butterworths, 1987, 582 pp, \$54.95.

Thomas ST, ed. *Cardiovascular Anesthesia*. Vol 1, No. 3 in Problems in Anesthesia Series. Philadelphia: JB Lippincott, 1987, 194 pp, \$25.00 single copy or \$55.00 for annual subscription.

Waughman WR, Rigor BM, Katz LE, Garda JF, Bradshaw HW. *Principles and Practice of Nurse Anesthesia*. Norwalk, CT: Appleton & Lange, 1987, 688 pp, \$79.95.

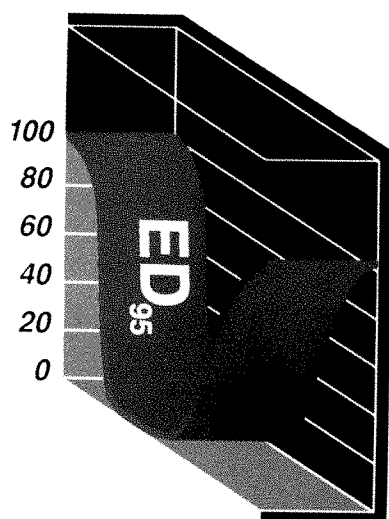
Wildsmith JA, Armitage EN. *Principles and Practice of Regional Anesthesia*. New York: Churchill Livingstone, 1987, 200 pp, \$65.00.

William G. *The Age of Miracles*. Chicago: Academy Chicago Publishers, 1987, 234 pp, \$8.95 (paper) or \$16.95 (cloth).



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**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it. **WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

### PRECAUTIONS:

**General:** Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

### ADVERSE REACTIONS:

**Observed in Controlled Clinical Studies:** Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%.


Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of  $\geq 0.60$  mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses  $\leq 0.30$  mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

**Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: **General:** allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); **Musculoskeletal:** inadequate, prolonged block; **Cardiovascular:** hypotension, vasodilatation (flushing), tachycardia, bradycardia; **Respiratory:** dyspnea, bronchospasm, laryngospasm; **Integumentary:** rash, urticaria, injection site reaction

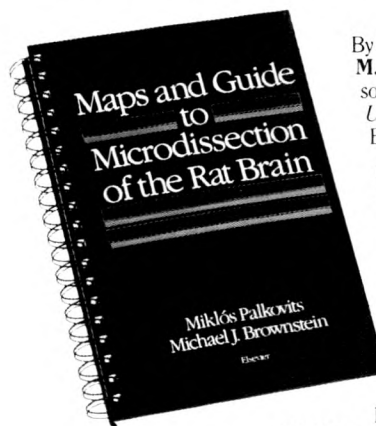
<sup>1</sup>Hughes R: Atracurium: An Overview. *Br J Anaesth* 1986;58:2s-4s.

<sup>2</sup>Payne J: Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*. Orlando, Grune & Stratton, 1984, p 98.

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# Maps and Guide to Microdissection of the Rat Brain



By **MIKLÓS PALKOVITS, M.D., PH.D., D.SCI.**, Professor of Anatomy, *Semmelweis University Medical School*, Budapest, Hungary

**MICHAEL J. BROWN-STEIN, M.D., PH.D.**, Chief, Laboratory of Cell Biology, *National Institute of Mental Health*, Bethesda, Maryland

An exceptional tool for the laboratory, **MAPS AND GUIDE TO MICRODISSECTION OF THE RAT BRAIN** describes techniques for the dissection, identification, and removal of brain nuclei.

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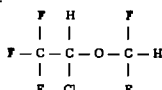
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### DESCRIPTION

FORANE (isoflurane, USP) is a nonflammable liquid administered by vaporizing, as a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants are:

Molecular weight	194.5
Boiling point at 760 mm Hg	48.5 °C (119 °F)
Refractive index $n_D^{20}$	1.2890-1.3005
Specific gravity 25 °/25 °C	1.486
Vapor pressure in mm Hg*	20 °C 239 25 °C 286 30 °C 357 35 °C 450

\*Equation for vapor pressure calculation:

$$\log_{10} P_{\text{vapor}} = A + \frac{B}{T} \quad \text{where: } A = 8.056 \\ B = -1684.56 \\ T = ^\circ\text{C} + 273.15 \text{ (Kelvin)}$$

Partition coefficients at 37 °C

Vetolipase	0.81
Blood/gas	1.43
Oil/gas	90.9

Partition coefficients at 25 °C - rubber and plastic

Conductive rubber/gas	62.0
Butyl rubber/gas	79.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5

Purity by gas chromatography

Lower limit of flammability in oxygen or nitrous oxide at 9 psi/psiac and 23 °C

Lower limit of flammability in oxygen or nitrous oxide at 900 psi/psiac and 23 °C

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight for 24 hours, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle light were UV light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

### CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N <sub>2</sub> O
20 ± 4	1.28	0.86
44 ± 7	1.18	0.80
64 ± 6	1.06	0.77

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a slight response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO<sub>2</sub>, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be obtained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE. THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

### INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

### CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

### WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

### PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP secretion, blood glucose and serum creatinine with decreases in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N<sub>2</sub>O.

### See CLINICAL PHARMACOLOGY.

Cardiogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 12, 18 and 132 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 16 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related teratogenic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO<sub>2</sub> absorption system (not constant). PaO<sub>2</sub> and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

### ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and flus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

### OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assured or controlled ventilation with pure oxygen.

### DOSEAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- vaporizers calibrated specifically for isoflurane;
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diffused. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ Isoflurane} = \frac{100 P_V P_V}{P_T (P_A - P_V)}$$

where: P<sub>A</sub> = Pressure of atmosphere  
P<sub>V</sub> = Vapor pressure of isoflurane  
F<sub>V</sub> = Flow of gas through vaporizer (mL/min)  
F<sub>T</sub> = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypoxic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

### HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0338

Revised: 10-85

Anaquest Forane® (isoflurane, USP)



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Anesthesiologist BC/BE sought for three-member group serving modern 200-bed community hospital. Six CRNAs. 4,000 cases/year. All surgical subspecialties except cardiac. Regional trauma center. Moderate OB. Active new outpatient surgery unit within hospital. Community of 25,000 in mountains of Western Maryland. Close to four-season recreational opportunities. Position available January 1988, but will wait for right person. Salary first, leading to partnership. Send CV and references to: W.R. Hodges III, MD, Department of Anesthesia, Memorial Hospital and Medical Center, Cumberland, MD 21502.

### UNIVERSITY OF MISSOURI

Anesthesiologists needed at Assistant and Associate Professor levels. Must be Board certified or Board eligible. Duties include patient care, resident and medical student teaching, and research. Positions available at the University of Missouri Health Sciences Center. Interested applicants send a Curriculum Vitae to: G. W. N. Eggers Jr, MD, Professor and Chairman, Department of Anesthesiology, University of Missouri-Columbia, MO 65212.

### ANESTHESIOLOGIST

BE/BC needed for 200-bed modern community hospital in SW PA 60 miles NE of Pittsburgh. College town with excellent hunting, fishing, hiking, skiing. Young progressive medical staff. Anesthesia team: 4 MDs, 9 CRNAs. Excellent future. No open heart, neuro. Reply to Box KK44, c/o Anesthesia and Analgesia, 333 Cedar Street, New Haven, CT 06510.

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One full-time faculty position at the Assistant/Associate Professor level in expanding, young department with emphasis on teaching and research. Complete clinical services in one hospital. Prerequisites: fellowship year or equivalent training in subspecialty area; board eligibility; meet California license requirements; ability to write scholarly articles and have a genuine commitment to inquiry. Particular attention will be given to those having critical care training. Women and minorities are encouraged to apply. Send curriculum vitae, bibliography, and names of three references to John H. Eisele Jr, MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. Position open until filled but not later than February 29, 1988. We are an Equal Opportunity/Affirmative Action Employer.

### INDIANA

A position is available for a pediatric anesthesiologist at the assistant or associate professor level in the Department of Anesthesia, Indiana University School of Medicine. Candidates must have completed a specialized year in pediatric anesthesia and be in the examination system or board certified. Please send a curriculum vitae to

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Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum 1/4 page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: **\$1.00 per word, minimum twenty words. Additional fee of \$12.00 for box number ads.** Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be typed double-spaced and mailed in duplicate to:

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Robert K. Stoelting, M.D., Professor and Chairman, Department of Anesthesia, Fesler Hall Room 204, Indiana University School of Medicine, 1120 South Drive, Indianapolis, IN 46223.

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#### INDIANA

Faculty positions are available at the Assistant and Associate Professor levels for all aspects of adult anesthesia including pain management. All candidates for these positions must be in the examination system or board certified. Please send a curriculum vitae to Robert K. Stoelting, M.D., Professor and Chairman, Department of Anesthesia, Fesler Hall Room 204, 1120 South Drive, Indiana University School of Medicine, Indianapolis, IN 46223.

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#### OREGON

Oregon Health Sciences University, Department of Anesthesiology, is recruiting for faculty members at the Assistant and Associate Professor levels. Specialized year training or equivalent experience is required. Specific need exists in critical care, pediatric, obstetrical, and cardiac anesthesia but others with strong clinical teaching interest and ability will be considered. Research interest and background is desirable. Candidates must be eligible for Oregon Medical License. Please send C.V. and names of three references to Wendell C. Stevens, M.D., Department of Anesthesiology, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201. The Oregon Health Sciences University is an equal opportunity/affirmative action employer.

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#### MEDICAL COLLEGE OF WISCONSIN

An opportunity exists for a bright, personable anesthesiologist seeking a stimulating academic career. The Medical College of Wisconsin Department of Anesthesiology, an Affirmative Action Equal Opportunity Employer, has a teaching program with 50 residents, over 60 staff, and seven major teaching hospitals. The qualified applicant will find numerous avenues to pursue both clinical and basic science research. Our highly competitive residency program will assure a stimulating teaching environment. The Milwaukee area offers an abundance of cultural and recreational activities with an excellent educational system. If you desire the benefits of a large city while in an environment that preserves your quality of life, write to us discussing your abilities and strengths. Please include your curriculum vitae. Address replies to: Karel J. Kotrly, M.D., Department of Anesthesiology, 5000 W. National Ave., Milwaukee, WI 53295.

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#### MICHIGAN

Energetic and personable American graduate, BC/BE anesthesiologist needed to join

seven other anesthesiologists in a fee-for-service private practice. 400-plus-bed general hospital. All specialties with the exception of open heart. Send C.V. to Box LL45, *c/o Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

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#### MAINE

Excellent opportunity for BC/BE Anesthesiologist to join group practice at a 250-bed regional medical center in central Maine. Group includes four physicians and five CRNAs. All surgical subspecialties except OH. Construction program underway includes a new six-room O.R. suite and support facilities. Opportunity combines a professionally rewarding practice with a four-season area well known for its quality of life. Please reply Box LL46, *c/o Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

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#### ANESTHESIOLOGIST BC/BE

to join group of 10 MDs with CRNAs in a large hospital located in a pleasant mid-western community on the Great Lakes. Busy practice covering all major surgical subspecialties plus respiratory/ICU involvement and minimal OB. Excellent starting salary and benefits package leading to early partnership. Reply to Box LL47, *c/o Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

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#### ANESTHESIOLOGIST

Board certified/board eligible, to join a four-member incorporated group with CRNAs. 400-bed community hospital in Western Pennsylvania, close to large metropolitan areas. Excellent schools, recreational facilities, friendly community. All types of anesthesia except open heart, minimal OB. Reply to: Box LL48 *c/o Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

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#### ANESTHESIOLOGIST: UPPER MIDWEST

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#### PEDIATRIC ANESTHESIOLOGIST

wanted for University Hospitals. Must be at least board eligible. Competitive salaries and benefits. Inquiries from minority candidates are encouraged. Send curriculum

vitae to Helmut F. Cascorbi, M.D., Ph.D., Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

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#### UNIVERSITY HOSPITALS OF CLEVELAND

Department of Anesthesiology is recruiting faculty for University Hospitals and affiliated hospital. Candidates with specialty training in pediatric anesthesiology or pain management preferred. Must be at least board eligible. Competitive salaries and benefits. Inquiries from minority candidates are encouraged. Send curriculum vitae to Helmut F. Cascorbi, M.D., Ph.D., Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

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A seminar for anesthesia residents and recent graduates in anesthesia sponsored by Beth Israel Medical Center and Mount Sinai School of Medicine, will take place on Saturday, March 19, 1988, at Beth Israel Medical Center in New York. For further information write or call Dr. Isaac Azar, (212) 420-2385.

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are encouraged to apply. Send curriculum vitae, bibliography, and names of three references to John H. Eisele, Jr., M.D., Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. Position open until filled but not later than October 31, 1988. We are an Equal Opportunity/Affirmative Action Employer.

#### ARIZONA

The Department of Anesthesiology at the University of Arizona College of Medicine has openings for both clinical and tenure track faculty. Female and minority applicants are welcome. Applicants interested in an academic career should contact: Burnell R. Brown Jr, M.D., Ph.D., Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ 85724. Equal Employment Opportunity/Affirmative Action Employer. Closing date: 6/30/88.

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#### ANESTHESIOLOGY RESIDENTS

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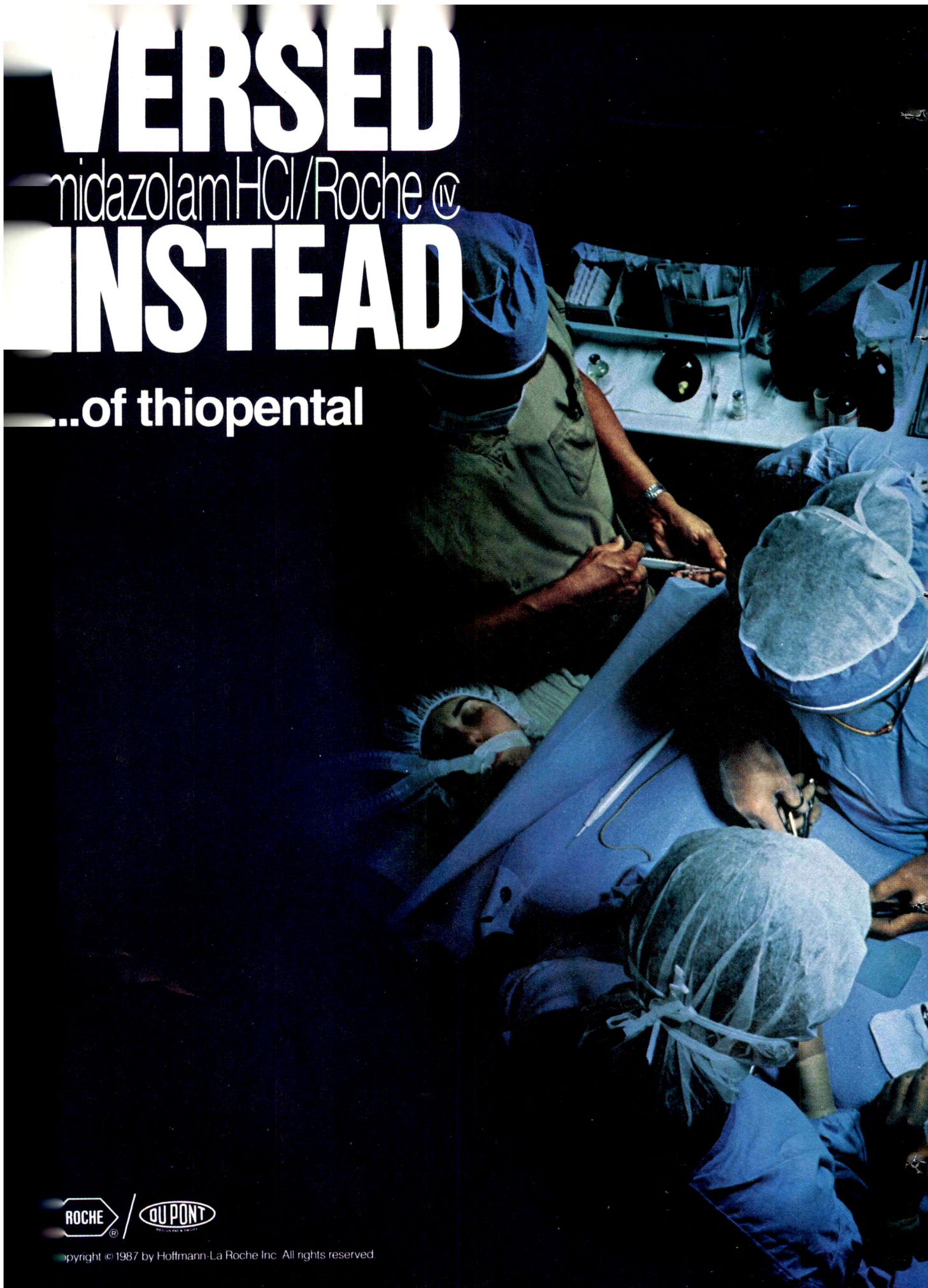


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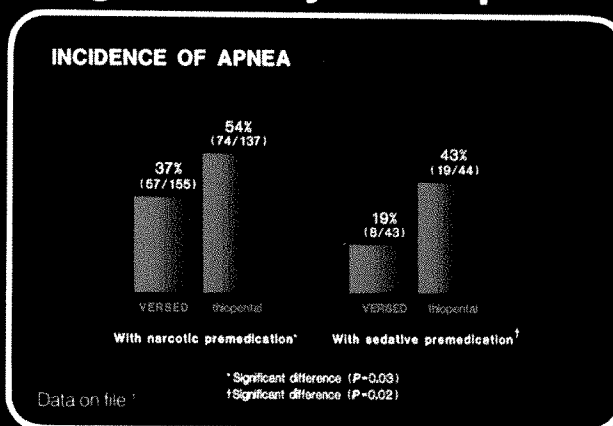
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Please see references and summary of product information on the following page



**References:** 1. Data on file (Doc. #069-005, 007), Roche Laboratories. 2. VERSED® (brand of midazolam HCl/Roche) ©, Scientific Summary, Roche Laboratories, a division of Hoffmann-La Roche Inc., Nutley, NJ, 1986.

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**Before prescribing, please consult complete product information, a summary of which follows:**

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

**CONTRAINDICATIONS:** Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma, may be used in open angle glaucoma only if patients are receiving appropriate therapy. **WARNINGS:** Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

**Usage in Pregnancy:** An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

**PRECAUTIONS:** General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

**Information for patients:** Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant.

**VERSED® (brand of midazolam HCl/Roche)**

3. Inform your physician if you are nursing

**Drug interactions:** The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

**Drug/laboratory test interactions:** Midazolam has not been shown to interfere with clinical laboratory test results.

**Carcinogenesis, mutagenesis, impairment of fertility:** Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

**Pregnancy:** Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

**Labor and delivery:** Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

**Nursing mothers:** It is not known whether midazolam is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

**Pediatric use:** Safety and effectiveness in children below the age of 18 have not been established.

**ADVERSE REACTIONS:** See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

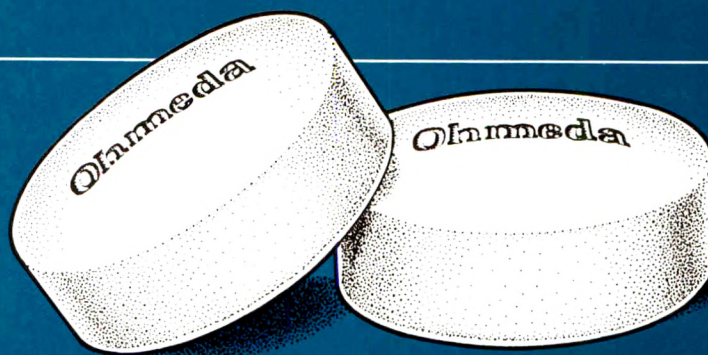
Following IM injection: headache (1.3%), local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%), local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration. **Respiratory:** Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. **Cardiovascular:** Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. **Gastrointestinal:** Acid taste, excessive salivation, retching. **CNS/Neuromuscular:** Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. **Special Sense:** Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. **Integumentary:** Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. **Miscellaneous:** Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma. **Drug Abuse and Dependence:** Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

**OVERDOSAGE:** Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

**DOSAGE AND ADMINISTRATION:** VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam.

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**WARNINGS**—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and anti-shock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

**Use in Pregnancy**—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

**ADVERSE REACTIONS**—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

**DOSAGE AND ADMINISTRATION**—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg/kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

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1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975
2. Ravin MB: Pyridostigmine as an antagonist of d-tubocurarine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg*—*Curr Res* 54:317-321, 1975.



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# Soon...the emergence of a new era in anesthesiology

For nearly five decades, Stuart Pharmaceuticals has been an innovative force in professional health care—with significant contributions to the fields of cardiology, oncology, infectious disease, and gastroenterology. And now, Stuart Pharmaceuticals innovation continues into the demanding field of anesthesiology.

The challenges of today's surgery call for a new era in anesthesiology. Soon, with an important introduction from Stuart Pharmaceuticals, that new era will be here.



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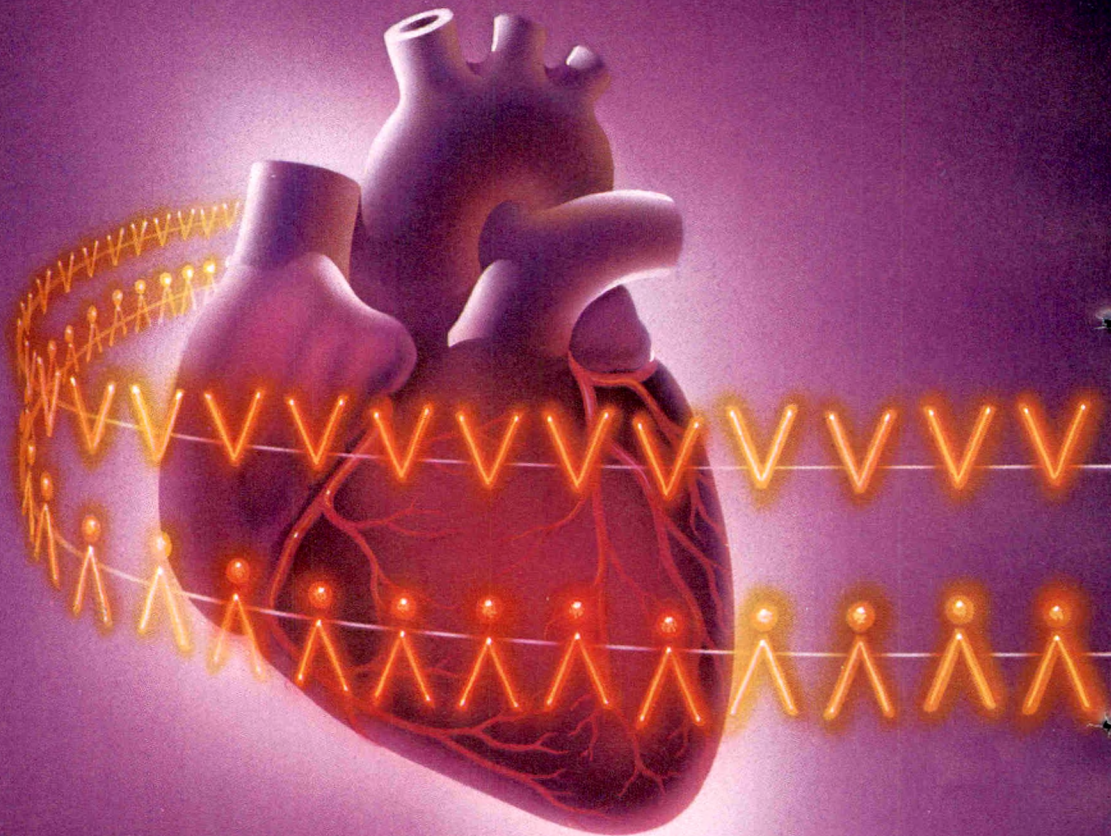
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Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

**CAUTION:** Federal Law Prohibits Dispensing Without Prescription.

**DESCRIPTION:** SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50  $\mu\text{g}$  per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

**INDICATIONS AND USAGE:** SUFENTA (sufentanil citrate) is indicated: As an analgesic adjunct in the maintenance of balanced general anesthesia. As a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated. SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

**CONTRAINDICATIONS:** SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS:** SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to  $\frac{1}{4}$  of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8  $\mu\text{g}/\text{kg}$ , 2) administration of a full paralyzing dose of a neuromuscular blocking agent

following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8  $\mu\text{g}/\text{kg}$ ) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8  $\mu\text{g}/\text{kg}$ ). The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

**PRECAUTIONS: General:** The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. Vital signs should be monitored routinely. Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY). The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to  $\text{CO}_2$  stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area. Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced. Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries. Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion



# THE PRIMARY ANESTHETIC THAT KEEPS PATIENTS ON TRACK

## SUFENTA<sup>®</sup> (sufentanil citrate) Injection

Predictable control for longer, more stressful procedures

**PROVIDES** smooth induction<sup>1</sup>

**BLUNTS** hemodynamic response to intubation  
and surgical stimulation<sup>2</sup>

**REDUCES** need for vasoactive drugs in  
the intraoperative and postoperative periods<sup>1</sup>

**RESULTS** in lower postoperative morbidity after  
aortic surgery compared with isoflurane<sup>3</sup>  
(in a randomized study comparing sufentanil and isoflurane)

**CONVENIENT:** Fewer ampoules to open

of SUFENTA.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

**Pregnancy Category C:** SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

**Animal Toxicology:** The intravenous LD<sub>50</sub> of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

**ADVERSE REACTIONS:** The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%). Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia  
Gastrointestinal: nausea, vomiting  
Respiratory: apnea, postoperative respiratory depression, bronchospasm

Dermatological: itching, erythema  
Central Nervous System: chills  
Miscellaneous: intraoperative muscle movement

**DRUG ABUSE AND DEPENDENCE:** SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

**OVERDOSAGE:** Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD<sub>50</sub> of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD<sub>50</sub>s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

**DOSEAGE AND ADMINISTRATION:** The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).



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Piscataway, NJ 08854

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U.S. Patent No. 3,998,834  
7616504-M

January 1986, March 1986  
JPI-710



*Too deep? Too light?*  
**Now you can accurately  
monitor anesthetic depth**

with the  
**LECTRON 302**  
Esophageal Monitor



The smooth muscle of the lower esophagus is an ideal indicator of anesthetic depth because it is directly connected to the brain stem via the vagus nerve and is not affected by paralyzing agents. As a result, esophageal activity can be measured throughout surgery.<sup>1,2</sup> Changes in brain stem activity are reflected in the frequency and strength of lower esophageal contractility (LEC); it increases as anesthesia lightens and decreases as it deepens.<sup>3</sup> The Lectorn 302 uses a disposable esophageal probe, equipped with two balloons, to easily and accurately monitor LEC for more precise control of anesthetic depth.

*Secondary PLEC contractions occur in response to inflation of proximal balloon.<sup>4</sup>*

*Distal saline-filled balloon measures the rate of spontaneous LEC (SLEC) and the amplitude of provoked LEC (PLEC).<sup>4</sup>*

*The probe is connected to the patient station. A pressure transducer on the station measures the amplitude of PLECs and counts the number of SLECs.*



# The LECTRON 302

## MULTIPURPOSE ESOPHAGEAL MONITOR

### A totally new concept in the assessment of anesthetic depth

The Lectron 302 Monitor allows the titration of the minimum anesthetic dose for each patient while still providing adequate depth.<sup>5</sup> It monitors spontaneous and provoked lower esophageal contractions (SLEC and PLEC), which are sensitive indicators of anesthetic depth, sharing an inverse relationship to increasing MAC.<sup>5,6,7</sup> SLEC is more frequent under light anesthesia than under deeper anesthesia, while PLEC becomes more forceful as anesthesia lightens.<sup>3</sup>

**For information about a complimentary 15-day trial please call 1-800-423-2761**

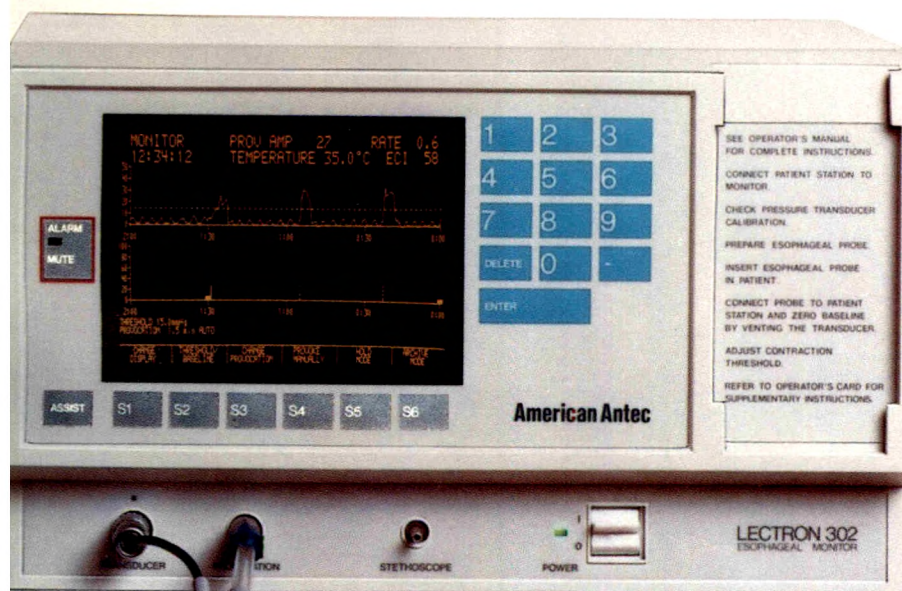
Try the Lectron 302 Esophageal Monitor in your hospital for 15 days. See for yourself how it can help you maintain optimal anesthesia levels for your patients. There is no charge or obligation.

**Call today or write**

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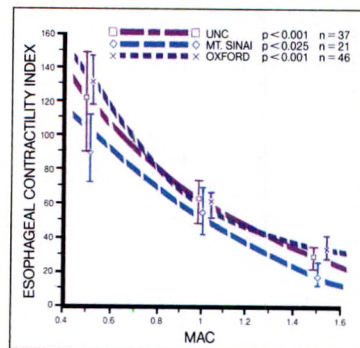
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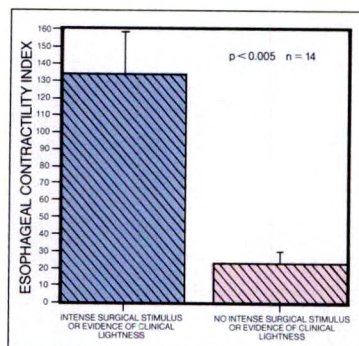
*The Lectron 302 Monitor displays the rate of SLEC and the amplitude of PLEC. It also functions as an esophageal stethoscope, displays core body temperature and provides a ventilator disconnect alarm.*

**These figures demonstrate the strong relationship between LEC and anesthetic depth.**



**LEC vs. MAC**

*The combined spontaneous LEC rate and the provoked LEC amplitude is a sensitive indicator of anesthetic depth.*



**LEC vs. Surgical Stimuli**

*The sensitivity of LEC to surgical stimuli shows a dramatic difference between adequate and inadequate anesthesia levels.*

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**American Antec, Inc.**

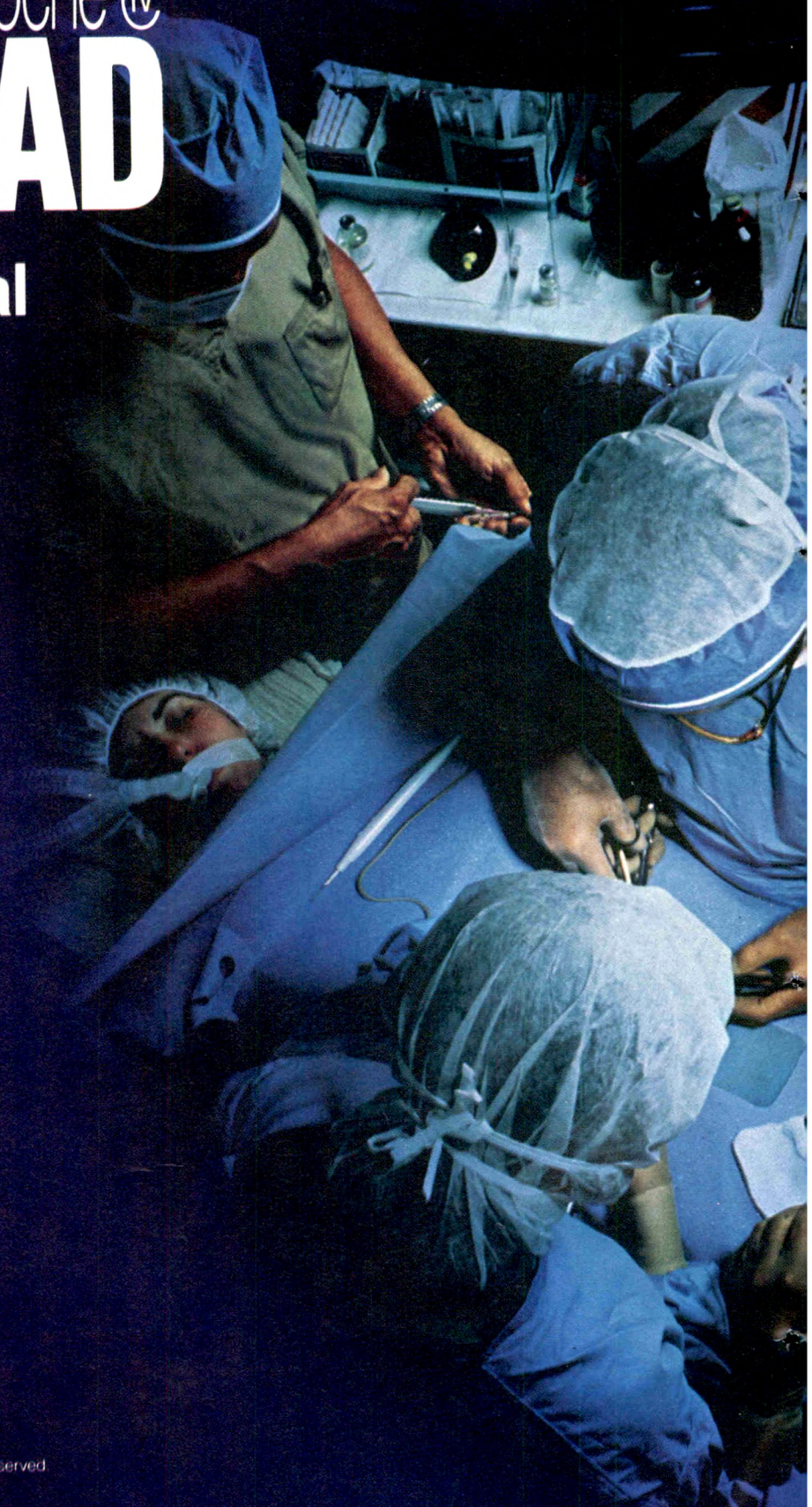


# VERSED

nidazolam HCl/Roche <sup>®</sup> IV

# INSTEAD

...of thiopental



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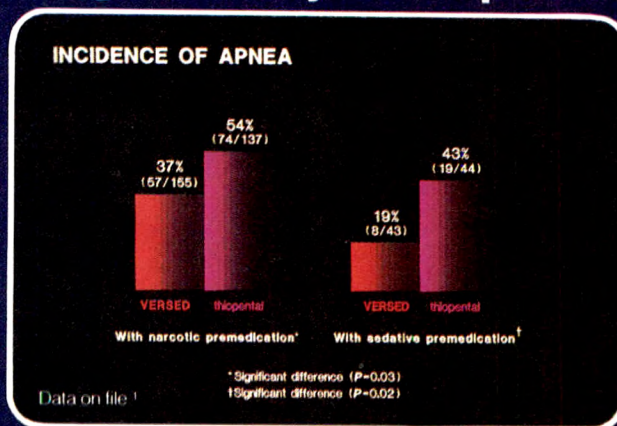
DUPONT

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## Key advantages in induction

- **Significantly less apnea**



- **Better hemodynamic stability**

While differences were not statistically significant, VERSED IV produced less pronounced decreases in stroke volume, heart rate, cardiac output and systemic vascular resistance... and a less pronounced increase in mean right atrial pressure<sup>2</sup>

- **Pronounced anterograde amnesia**

Significantly more VERSED-treated patients (24/24) had complete or partial anterograde amnesia than did thiopental-treated patients (13/26)<sup>1</sup>

As a standard precaution, prior to IV administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and familiar with all dosing and administration guidelines. Reduce dosage in elderly and debilitated, in patients receiving narcotic premedication, and in those with limited pulmonary reserve.



INJECTABLE  
**VERSED**<sup>®</sup>  
brand of  
midazolam HCl Roche IV  
equivalent to 1 mg/mL or 5 mg/mL

**A significant advance in anesthetic induction**

Please see references and summary of product information on the following page.



**References:** 1. Data on file (Doc. #089-005, 007), Roche Laboratories. 2. VERSED® (brand of midazolam HCl/Roche) & Scientific Summary, Roche Laboratories, a division of Hoffmann-La Roche Inc., Nutley, NJ, 1986.

**VERSED®**  
(brand of midazolam HCl/Roche)®  
**INJECTION**

**Before prescribing, please consult complete product information, a summary of which follows:**

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

**CONTRAINDICATIONS:** Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy. **WARNINGS:** Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. **For conscious sedation, do not administer IV by rapid or single bolus.** Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combativeness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

**Usage in Pregnancy:** An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlorthalidone) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

**PRECAUTIONS:** General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

**Information for patients:** Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant.

**VERSED® (brand of midazolam HCl/Roche)**

3. Inform your physician if you are nursing.

**Drug Interactions:** The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

**Drug/Laboratory test Interactions:** Midazolam has not been shown to interfere with clinical laboratory test results.

**Carcinogenesis, mutagenesis, impairment of fertility:** Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

**Pregnancy:** Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

**Labor and delivery:** Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

**Nursing mothers:** It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

**Pediatric use:** Safety and effectiveness in children below the age of 18 have not been established.

**ADVERSE REACTIONS:** See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: **Respiratory:** Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. **Cardiovascular:** Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. **Gastrointestinal:** Acid taste, excessive salivation, retching. **CNS/Neuromuscular:** Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, atetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia. **Special Sense:** Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. **Integumentary:** Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. **Miscellaneous:** Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma. **Drug Abuse and Dependence:** Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

**OVERDOSAGE:** Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

**DOSAGE AND ADMINISTRATION:** VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. **BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.)** Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

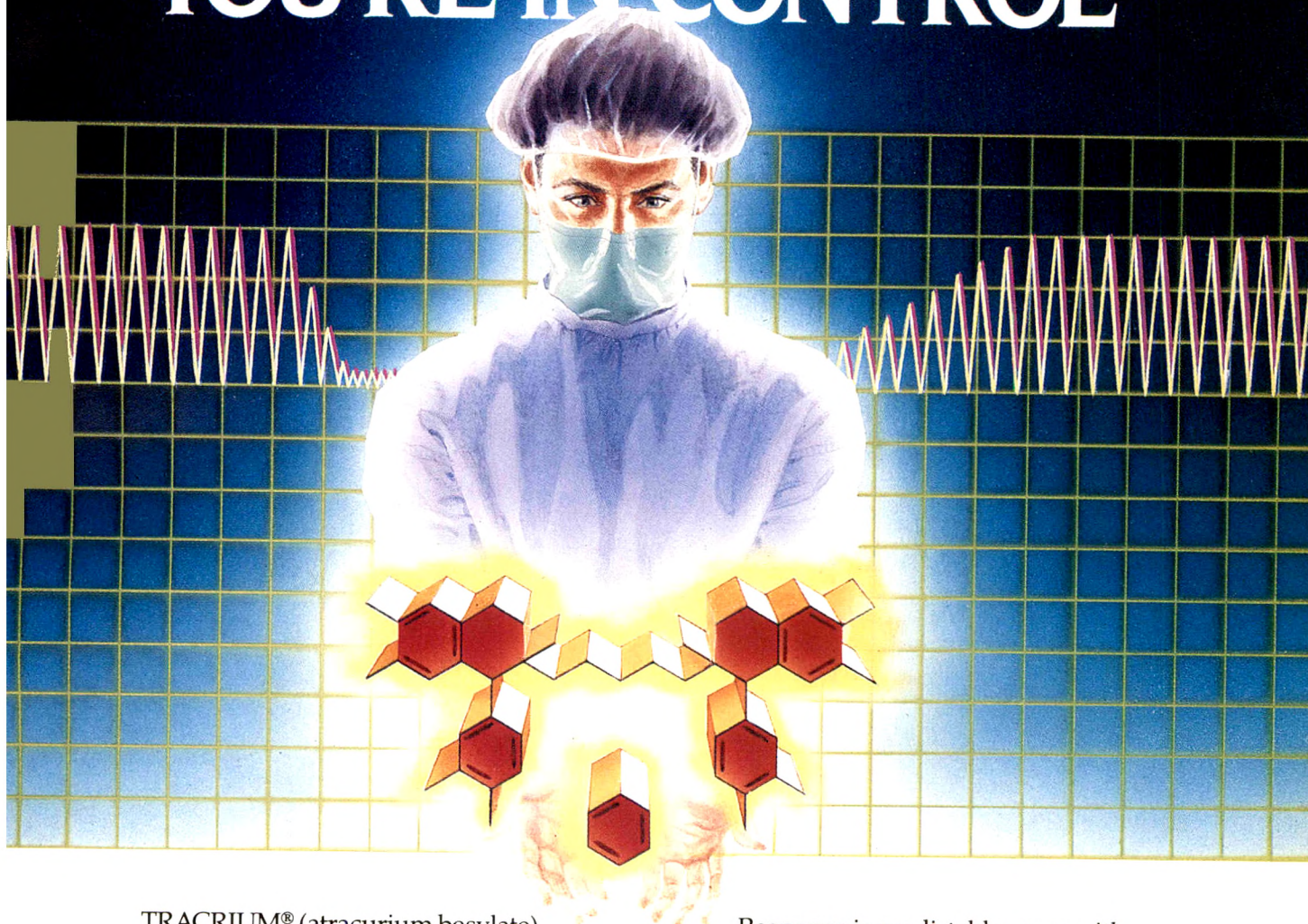
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## TRACRIUM® INJECTION

(atracurium besylate)



## TRACRIUM® INJECTION (atracurium besylate)

### Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

### PRECAUTIONS:

**General:** Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane, isoflurane, halothane, certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonistic effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

**Pregnancy, Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

### ADVERSE REACTIONS:

**Observed in Controlled Clinical Studies:** Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.3%.

Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of  $\geq 0.60$  mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses  $\leq 0.30$  mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

**Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: **General:** allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); **Musculoskeletal:** inadequate, prolonged block; **Cardiovascular:** hypotension, vasodilatation (flushing), tachycardia, bradycardia; **Respiratory:** dyspnea, bronchospasm, laryngospasm; **Integumentary:** rash, urticaria, injection site reaction.

<sup>1</sup>Miller F, Rupp S, Fisher D, et al: Clinical pharmacology of vecuronium and atracurium. *Anesth* 1984;61:444-453.

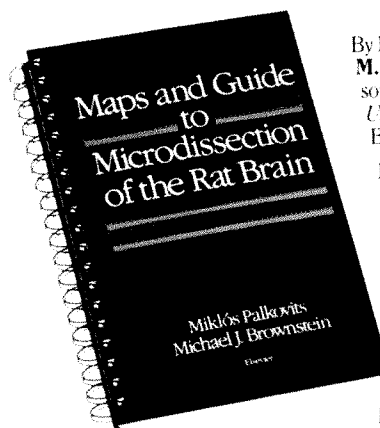
<sup>2</sup>Payne J. Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*. Orlando, Grune & Stratton, 1984, p 98.

<sup>3</sup>Eagar E, Flynn P, Hughes R: Infusion of atracurium for long surgical procedures. *Br J Anaesth* 1984;56:447-452.



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# Maps and Guide to Microdissection of the Rat Brain



By **MIKLÓS PALKOVITS, M.D., PH.D., D.SCI.**, Professor of Anatomy, *Semmelweis University Medical School*, Budapest, Hungary

**MICHAEL J. BROWN-STEIN, M.D., PH.D.**, Chief, Laboratory of Cell Biology, *National Institute of Mental Health*, Bethesda, Maryland

An exceptional tool for the laboratory. **MAPS AND GUIDE TO MICRODISSECTION OF THE RAT BRAIN** describes techniques for the dissection, identification, and removal of brain nuclei.

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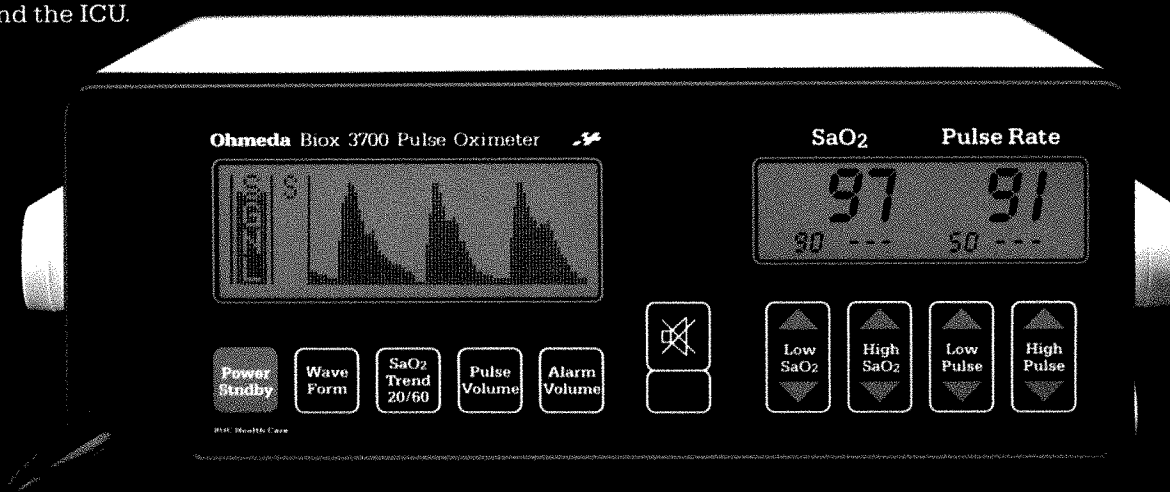
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# 3700 vs. 3740

In oximetry, we're our own competition. Our full-featured 3700 was designed to meet the special demands for oxygenation monitoring in the OR, while the 3740 has just the features you need for the Post Anesthesia Care Unit and the ICU.

Most importantly, both the 3700 and 3740 incorporate a waveform. And frankly, without a waveform, pulse oximetry just isn't pulse oximetry.

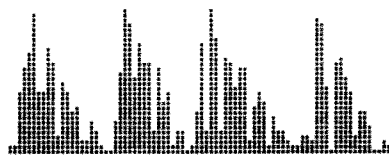


"As in capnography, a waveform is desirable because it helps you distinguish between artifact information and real information."

Nikolaus Gravenstein, M.D.  
Department of Anesthesiology  
College of Medicine  
University of Florida  
Gainesville, Florida



In the presence of a clean, physiological signal, the waveform is smooth, uniform and pulsatile in shape.



With interference, the waveform shows a noisy plethysmograph.

The reason: interference is a documented phenomenon in SaO<sub>2</sub> monitoring.<sup>1,2,3</sup> If undetected, erroneous SaO<sub>2</sub> readings may result.

The combination of Ohmeda's Waveform Display and Signal Strength Indicator provides a unique system for quality control assessment of the pulsatile signal by verifying optimal

probe placement, validating SaO<sub>2</sub> readings, and detecting interference.

## The Ohmeda Biox 3700 Pulse Oximeter.

It's the world's foremost pulse oximeter for use in the critical environment of the OR.

It has two separate continuous displays—one for SaO<sub>2</sub> and pulse rate readings, and a dedicated graphic display for our exclusive Waveform, Signal Strength Indicator, and trend display.

In addition, the 3700 uses intelligent signal processing techniques based on thirty

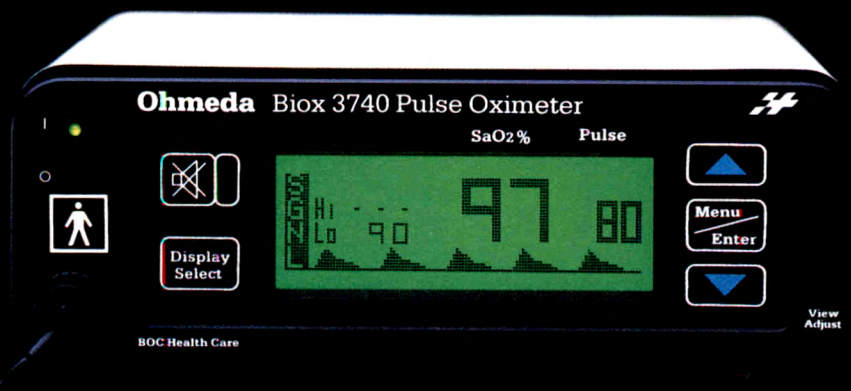
<sup>1</sup>Block FE Jr, MD: "Interference in a Pulse Oximeter from a Fiberoptic Light Source." *Journal of Clinical Monitoring* 3:3:210-211, July 1987.

<sup>2</sup>"Pulse Oximeter Interference from Surgical Lighting." *Health Devices* 16:2:50-51, February 1987.

<sup>3</sup>Brooks TD, MD; Paulus DA, MS, MD; Winkle WE, BMET: Letter to the Editor: "Infrared Heat Lamps Interfere with Pulse Oximeters." *Anesthesiology* 61:5:630, November 1984.

<sup>4</sup>Palve H, Vouri A: Pulse Oximetry Forum, abstracted, The Central European Anesthesia Congress, Munich, Germany, September 17, 1987.

# Either way you win. Ohmeda Waveform Pulse Oximetry.



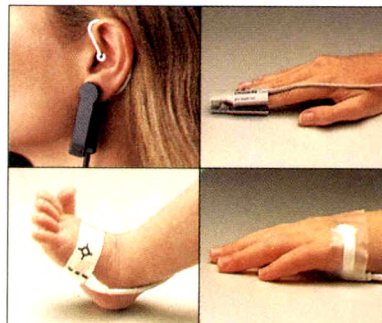
SaO<sub>2</sub> calculations per second to minimize the effect of interference.

## The new Ohmeda Biox 3740 Pulse Oximeter.

Our new, compact, portable 3740 maintains the quality and essential features of the 3700, with the convenience of a single liquid crystal display.

It features our Waveform and Signal Strength Indicator in two selectable displays: numeric-dominant with large SaO<sub>2</sub> readings for routine monitoring, or waveform-dominant for optimal probe site selection and interference detection.

The 3740's intelligent signal processing techniques provide superior motion rejection—without the bother of ECG leads—and allow for accurate readings on poorly perfused, “shocky” patients.<sup>4</sup>



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# For outpatient anesthesia



## Rapid

Well-suited to the rapid turnover of outpatient cases, the low solubility of isoflurane in blood and tissue (only that of nitrous oxide is lower) enables you to quickly adjust the level of anesthesia to patient and surgical requirements.

Following anesthesia, a rapid washout and prompt recovery provide for your early patient assessment. Patient alertness and cooperation can facilitate handling in the outpatient setting.

## Complete

Without any other agent or premedicant, isoflurane provides every action required for a complete anesthetic, on a closely controlled, breath-by-breath basis: unconsciousness, surgical analgesia, amnesia, and good surgical muscle relaxation—a useful advantage for laparoscopies and orthopedic work, and one that begins when the anesthetic begins and ends with elimination of the anesthetic, thereby decreasing the risk of residual paralysis in the PAR.

Because isoflurane is a complete anesthetic when given alone in oxygen or room air, *nitrous oxide can be eliminated* if you choose. Isoflurane anesthetics are seldom complicated and prolonged by postoperative nausea and vomiting.



# FORANE<sup>®</sup> (isoflurane, USP)



## Excellent Safety Profile

Stability of heart rhythm and good cardiac output are notable features of an isoflurane anesthetic. CNS excitation does not occur at any concentration or  $\text{PaCO}_2$  level. Virtually 100% of isoflurane is exhaled unchanged from the patient (only 0.17% of the isoflurane taken up is recovered as metabolites). This near absence of metabolic by-products all but assures an absence of hepatic or renal toxicity from metabolism.

# Anaquest



# For outpatient anesthesia

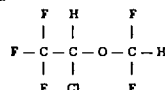
# FORANE® (isoflurane, USP)

## Rapid...Complete...Excellent Safety Profile

CAUTION: Federal Law Prohibits Dispensing without Prescription.

### DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants are:

Molecular weight	184.5
Boiling point at 760 mm Hg	48.5 °C (uncorr.)
Refractive index $n_D^{20}$	1.2990-1.3005
Specific gravity 25 °/25 °C	1.498
Vapor pressure in mm Hg**	20 °C 238
	25 °C 295
	30 °C 367
	35 °C 450

\*\*Equation for vapor pressure calculation:

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where: } A = 8.066$$

$$B = -1654.18$$

$$T = ^\circ\text{C} + 273.15 \text{ (Kelvin)}$$

Partition coefficients at 37 °C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	80.8

Partition coefficients at 25 °C - rubber and plastic

Conductive rubbers/gas	52.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%

Lower limit of flammability in oxygen or

nitrous oxide at 9 joules/sec. and 23 °C	None
--	------

Lower limit of flammability in oxygen or

nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthetics.
--	---

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, mostly ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave UV light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

### CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N <sub>2</sub> O
25 ± 4	1.28	0.66
44 ± 7	1.15	0.80
64 ± 5	1.06	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a high response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO<sub>2</sub>, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypotension which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthetic period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

### INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

### CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

### WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortion.

FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

### PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient. Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decreases in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N<sub>2</sub>O.

### See CLINICAL PHARMACOLOGY.

Cardiopulmonary Swine: ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untested control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 8 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc. An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO<sub>2</sub> absorption system (not certain). PaO<sub>2</sub> and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-bicarbonate-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

### ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiological effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and flus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

### OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

### DOSEAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- vaporizers calibrated specifically for isoflurane;
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ Isoflurane} = \frac{100 F_V P_V}{F_T (P_A - P_V)}$$

where:  $P_A$  = Pressure of atmosphere  
 $P_V$  = Vapor pressure of isoflurane  
 $F_V$  = Flow of gas through vaporizer (mL/min)  
 $F_T$  = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

### HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10018-380-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0336

Revised 10-85

# Anaquest Forane® (isoflurane, USP)

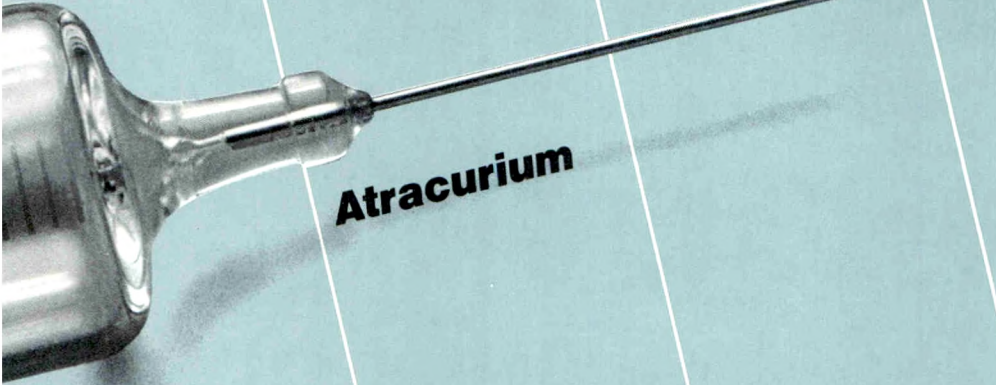


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**In neuromuscular  
blockade:  
Greater safety  
begins where the  
similarities end.**



**Atracurium**

A close-up photograph of a glass syringe with a needle, angled diagonally across the frame. The syringe is partially filled with a clear liquid. The needle is sharp and pointed towards the upper right. The background is a solid light blue color.



**Norcuron<sup>®</sup>**  
(vecuronium bromide) for injection

A close-up photograph of a glass syringe with a needle, angled diagonally across the frame. The syringe is partially filled with a clear liquid. The needle is sharp and pointed towards the upper right. The background is a solid light blue color.

See last page for brief summary of prescribing information on NORCURON<sup>®</sup>.





## **The similarities:**

Short, intermediate, and long procedures.

Continuous infusion.

## **The Norcuron<sup>®</sup> difference:**

Free of clinically significant cardiovascular effects.

High-dose safety.



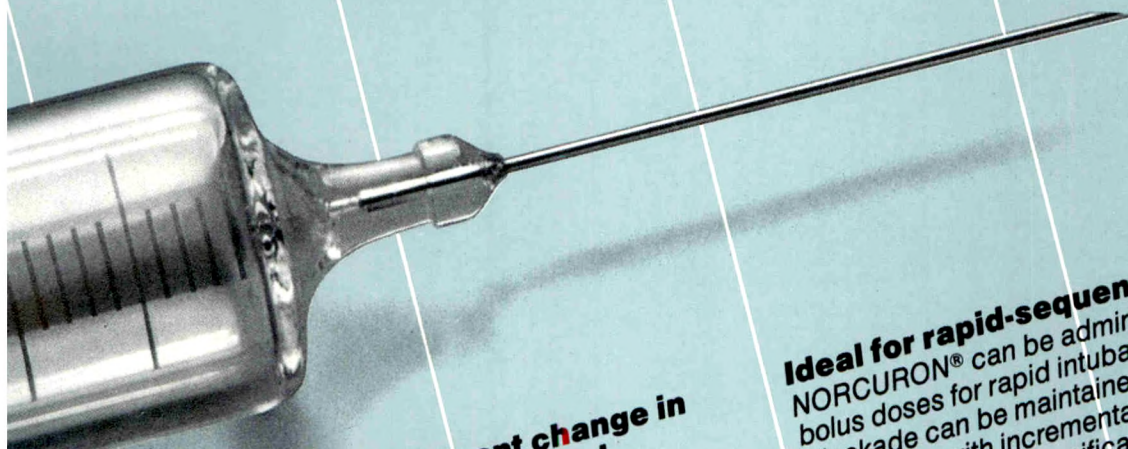
**Polypharmacy  
avoided.**

**Histamine  
release  
unlikely.**

**No  
refrigeration.**

**Stability/  
potency  
assured.**

**Free from  
potentially  
toxic  
metabolites.**



**Little risk of significant change in  
heart rate and arterial blood  
pressure.**

Even at  $3.5 \times ED_{95}$ , there is a wide safety margin between assayed plasma histamine concentrations and levels at which significant changes in arterial pressure and heart rate are known to occur.<sup>1,2</sup>

**Choose the technique you  
prefer for longer procedures.**

Either continuous infusion for smooth, steady-state relaxation or high initial bolus dosing.

**For virtually all your patients.**

The only neuromuscular blocking agent virtually free of clinically significant cardiovascular and histamine-related side effects.<sup>1,3-6</sup> For patients with significant cardiovascular disease, asthmatics and others in whom substantial histamine release would be hazardous, the elderly, infants, and outpatients.

**Ideal for rapid-sequence induction.**  
NORCURON® can be administered in high bolus doses for rapid intubation,<sup>7</sup> and blockade can be maintained throughout the procedure with incremental doses of the same agent. This significantly simplifies dosing, monitoring, and administration and avoids the complications of polypharmacy.

Since atracurium cannot be easily administered in high doses without risk of histamine-related side effects, use of an additional agent is usually required for rapid intubation.<sup>8</sup>

**Room temperature stability.**

No refrigeration required. Lyophilized NORCURON® reconstituted at surgery assures optimal potency;

See next page for brief summary of  
prescribing information on NORCURON®.

**Norcuron®** where safety begins.  
(vecuronium bromide) for injection



# Norcuron® (vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

**THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.**

**CONTRAINDICATIONS:** None known.

**WARNINGS:** NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

**PRECAUTIONS:** Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for nonoperative surgery, a lower initial dose of Norcuron® should be considered.

**Altered Circulation Time:** Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

**Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

**Severe Obesity or Neuromuscular Disease:** Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

**Malignant Hyperthermia:** Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold, or cerebation. Administration must be accompanied by adequate anesthesia.

**Drug Interactions:** Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04 to 0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25 to 30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

**Inhalational Anesthetics:** Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

**Antibiotics:** Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B, colistin; and sodium colistimethate.

**Other:** Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

**Drug/Laboratory Test Interactions:** None known.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy:** Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

**Pediatric Use:** Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1 1/2 times as long to recover. Information presently available does not permit recommendations for use in neonates.

**ADVERSE REACTIONS:** Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

**OVERDOSAGE:** There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates, and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate, will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, cardiomyopathy, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

**DOSAGE AND ADMINISTRATION:** Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED<sub>50</sub>) given as an

Norcuron® (vecuronium bromide) for injection

intravenous bolus injection. This dose can be expected to produce good or excellent nonemergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25 to 30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45 to 65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg. Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04 to 0.06 mg/kg with inhalation anesthesia and 0.06 to 0.08 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg to 0.20 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained. Use by Continuous Infusion: After an intubating dose of 80 to 100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20 to 40 minutes later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations.

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 50% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25 to 60%, 45 to 60 minutes after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringer's. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035	
0.8	0.008	0.0040	
0.9	0.009	0.0045	
1.0	0.010	0.0050	
1.1	0.011	0.0055	
1.2	0.012	0.0060	
1.3	0.013	0.0065	

\*10 mg of Norcuron® in 100 mL solution.

†20 mg of Norcuron® in 100 mL solution.

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® Infusion Rate (mL/min)							
Amount of Drug (µg/kg/min)	Patient Weight (kg)						
	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

Note: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

**Dosage in Children:** Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1 1/2 times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore no dosing recommendation can be made.

**COMPATIBILITY:** Norcuron® (vecuronium bromide) for injection is compatible in solution with:

0.9% NaCl solution  
5% glucose in water  
5% glucose in saline  
Lactated Ringer's  
Sterile water for injection

Use within 8 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**HOW SUPPLIED:** 10 mL vials (10 mg of vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP), 22 g 1 1/4" needle. Boxes of 10 (NDC #0052-0441-60).

5 mL vials (10 mg vecuronium bromide) and 5 mL vials of diluent (bacteriostatic water for injection, USP).

Boxes of 10 (NDC #0052-0440-17).

10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP).

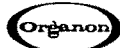
Boxes of 10 (NDC #0052-0441-17).

10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED. Boxes of 10 (NDC #0052-0441-15).

Rev. 1/89

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**References:** 1. Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 58:A273. 2. Scott RPF, Severance JJ: The cardiovascular and autonomic effects of neuromuscular blocking agents. *Semin Anesth* 1984; 3:319-334. 3. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary bypass grafting. *Anesthesiology* 1983; 58:438-440. 4. Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. 5. Durant NH: NORCURON® a new nondepolarizing blocking agent. *Semin Anesth* 1982; 1:47-56. 6. Krieg N, Cruz JF, Boell LHD: Relative potency of Org NC45, pancuronium, alcuronium and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. 7. Lennon RL, Olson RA, Gronert GA: Atacurium or vecuronium for rapid sequence endotracheal intubation. *Anesthesiology* 1986; 84:510-513. 8. Scott RPF, et al: Clinical pharmacology of atracurium given in high dose. *Br J Anaesth* 1986; 58:834-838.



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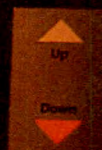
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# INTRAVENOUS NORMODYNE® (labetalol HCl) Injection

5 mg/mL



## Offers prompt and convenient blood pressure control...

### ■ Rapid response

Onset of action with NORMODYNE usually occurs within five minutes

### ■ Action is easily controlled

Helps avoid risk of "overshoot"

Postoperative blood pressure should be monitored during and following infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic pressure during intravenous treatment should be avoided.

In patients with excessive systolic hypertension, decrease in systolic pressure should be used as an indicator of therapeutic effectiveness...in addition to the response of diastolic pressure.

### ■ Easy administration

NORMODYNE may be used either by continuous infusion or by repeated IV injection

### ■ Cardiac output maintained

Helps assure vital organ perfusion

### ■ Helps prevent reflex tachycardia

### ■ Saves treatment time

—No intra-arterial monitoring needed

—No mixing required for IV injection

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. See **Drug Interactions** section of Brief Summary for full information.

Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume an upright position within three hours after intravenous administration of labetalol. Thus, the patient's ability to tolerate an orthostatic position should be established before permitting ambulation.

For Brief Summary, please see following page.

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World leader in drug delivery systems.



## PRODUCT INFORMATION

# NORMODYNE® brand of labetalol hydrochloride Injection

## BRIEF SUMMARY

### INDICATIONS AND USAGE

NORMODYNE (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.

### CONTRAINDICATIONS

NORMODYNE (labetalol HCl) Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia. (See **WARNINGS**.)

### WARNINGS

**Cardiac Failure** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

**In Patients Without a History of Cardiac Failure** In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, NORMODYNE (labetalol HCl) therapy should be withdrawn (gradually if possible).

**Ischemic Heart Disease** Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of NORMODYNE is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, NORMODYNE (labetalol HCl) administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

**Nonallergic Bronchospasm** (e.g., chronic bronchitis and emphysema) Since NORMODYNE (labetalol HCl) Injection at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

**Pheochromocytoma** Intravenous labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

**Diabetes Mellitus and Hypoglycemia** Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetes. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of anti-diabetic drugs.

**Major Surgery** The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Prolonged severe hypotension and difficulty in restarting or maintaining a heart beat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

**A synergism between labetalol HCl and halothane anesthesia has not been evaluated in this setting.**  
**Rapid Decreases of Blood Pressure** Caution must be observed when reducing severely elevated blood pressure. Although such findings have not been reported with intravenous labetalol HCl, a number of adverse reactions, including cerebral infarction, optic nerve infarction, angina and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as one or two days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

### PRECAUTIONS

**General Impaired Hepatic Function** may diminish metabolism of NORMODYNE (labetalol HCl) Injection.  
**Hypotension** Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving NORMODYNE (labetalol HCl) Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

**Jaundice or Hepatic Dysfunction** On rare occasions, oral labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately, should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

### Information for Patients

The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) NORMODYNE Injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on NORMODYNE Tablets, following adequate control of blood pressure with NORMODYNE Injection, appropriate directions for titration of dosage should be provided. (See **DOSAGE AND ADMINISTRATION**.)

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted: While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with NORMODYNE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with NORMODYNE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with NORMODYNE Tablets is initiated (see **ADVERSE REACTIONS**).

### Laboratory Tests

Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

### Drug Interactions

Since NORMODYNE (labetalol HCl) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia with labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

### Drug Laboratory Test Interactions

The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

### Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Nonteratogenic Effects

Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol HCl to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

### Labor and Delivery

Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

### Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when NORMODYNE (labetalol HCl) Injection is administered to a nursing woman.

### Pediatric Use

Safety and effectiveness in children have not been established.

## ADVERSE REACTIONS

NORMODYNE (labetalol HCl) Injection is usually well tolerated. Most adverse effects have been mild and transient and in controlled trials involving 92 patients did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving NORMODYNE (labetalol HCl) Injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with NORMODYNE Injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.  
Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin 7; hypoesthesia (numbness), and vertigo 1 each.  
Gastrointestinal System: Nausea in 13; vomiting 4; dyspepsia and taste distortion, 1 each.  
Metabolic Disorders: Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.  
Psychiatric Disorders: Somnolence/yawning in 3.  
Respiratory System: Wheezing in 1.  
Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see NORMODYNE Tablet Product Information for details). Certain of the side effects increased with increasing oral dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly dose related.

Labetalol HCl Daily Dose (mg)	200	300	400	600	800	900	1200	1600	2400
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	3	1	3	3	5	1	9	13	16
Fatigue	2	1	4	4	4	0	7	6	10
Nausea	<1	0	2	2	4	0	1	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Fathesthesia	2	0	2	2	1	1	2	5	5
Nasal Stuffiness	0	0	2	2	2	2	4	5	6
Ejaculation Failure	0	2	1	2	2	0	4	3	5
Impotence	1	1	1	1	2	0	3	4	3
Edema	1	0	1	1	1	0	1	2	2

The oculocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.

**Clinical laboratory tests:** Among patients dosed with NORMODYNE (labetalol HCl) Tablets, there have been reversible increases of serum transaminases in 4% of patients tested, and more rarely, reversible increases in blood urea.

## OVERDOSAGE

Overdosage with NORMODYNE (labetalol HCl) Injection causes excessive hypotension that is posture sensitive, and sometimes, excessive bradycardia. Patients should be placed supine and their legs raised if necessary to improve the blood supply to the brain. If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) may be useful for removal of the drug shortly after ingestion. The following additional measures should be employed if necessary: Excessive bradycardia — administer atropine or epinephrine. Cardiac failure — administer a digitalis glycoside and a diuretic. Dopamine or dobutamine may also be useful. Hypotension — administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. Bronchospasm — administer epinephrine and/or an aerosolized beta<sub>2</sub>-agonist. Seizures — administer diazepam.

In severe beta-blocker overdose resulting in hypotension and/or bradycardia, glucagon has been shown to be effective when administered in large doses (5 to 10 mg rapidly over 30 seconds, followed by continuous infusion of 5 mg/hr that can be reduced as the patient improves).

Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol HCl from the general circulation (<1%).

The oral LD<sub>50</sub> value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD<sub>50</sub> in these species is 50 to 60 mg/kg.

## DOSAGE AND ADMINISTRATION

NORMODYNE (labetalol HCl) Injection is intended for intravenous use in hospitalized patients. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

**Patients should always be kept in a supine position during the period of intravenous drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position should be established before permitting any ambulation, such as using toilet facilities.**

Either of two methods of administration of NORMODYNE Injection may be used: a) repeated intravenous injections, b) slow continuous infusion.

**Repeated Intravenous Injection:** Initially, NORMODYNE (labetalol HCl) Injection should be given in a dose of 20 mg labetalol HCl (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow intravenous injection over a two-minute period.

Immediately before the injection and at five and ten minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 mg or 80 mg can be given at ten minute intervals until a desired supine blood pressure is achieved or a total of 300 mg labetalol HCl has been injected. The maximum effect usually occurs within 5 minutes of each injection.

**Slow Continuous Infusion:** NORMODYNE (labetalol HCl) Injection is prepared for intravenous continuous infusion by diluting the contents with commonly used intravenous fluids (see below). Examples of methods of preparing the infusion solution are:

The contents of either two 20 ml vials (40 ml), or one 40 ml vial, are added to 160 ml of a commonly used intravenous fluid such that the resultant 200 ml of solution contains 200 mg of labetalol HCl, 1 mg/ml. The diluted solution should be administered at a rate of 2 ml/min to deliver 2 mg/min.

Alternatively, the contents of either two 20 ml vials (40 ml), or one 40 ml vial, of NORMODYNE (labetalol HCl) Injection are added to 250 ml of a commonly used intravenous fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2 mg/3 ml. The diluted solution should be administered at a rate of 3 ml/min to deliver approximately 2 mg/min.

The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion, the diluted solution can be infused using a controlled administration mechanism, e.g., graduated burette or mechanically driven infusion pump.

Since the half life of labetalol is 5 to 8 hours, steady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should then be stopped and oral labetalol HCl started (see below). The effective intravenous dose is usually in the range of 50 to 200 mg. A total dose of up to 300 mg may be required in some patients.

**Blood Pressure Monitoring:** The blood pressure should be monitored during and after completion of the infusion or intravenous injections. Rapid or excessive falls in either systolic or diastolic blood pressure during intravenous treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as indicator of effectiveness in addition to the response of the diastolic pressure.

**Initiation of Dosing with NORMODYNE (labetalol HCl) Tablets:** Subsequent oral dosing with NORMODYNE (labetalol HCl) Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 or 400 mg, depending on the blood pressure response. Thereafter, *inpatient titration* with NORMODYNE (labetalol HCl) Tablets may proceed as follows:

Regimen	Inpatient Titration Instructions	Daily Dose*
200 mg bid		400 mg
400 mg bid		800 mg
800 mg bid		1600 mg
1200 mg bid		2400 mg

\*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of NORMODYNE Tablets may be increased at one day intervals to achieve the desired blood pressure reduction.

For subsequent outpatient titration or maintenance dosing see NORMODYNE Tablets Product Information **DOSAGE AND ADMINISTRATION** for additional recommendations.

### Compatibility with commonly used intravenous fluids

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

NORMODYNE (labetalol HCl) Injection was tested for compatibility with commonly used intravenous fluids at final concentrations of 1.25 mg to 3.75 mg labetalol HCl per ml of the mixture. NORMODYNE Injection was found to be compatible with and stable (for 24 hours refrigerated or at room temperature) in mixtures with the following solutions:

Ringers Injection, USP  
Lactated Ringers Injection, USP  
5% Dextrose and Ringers Injection  
5% Lactated Ringers and 5% Dextrose Injection  
5% Dextrose Injection, USP  
0.9% Sodium Chloride Injection, USP  
5% Dextrose and 0.2% Sodium Chloride Injection, USP  
2.5% Dextrose and 0.45% Sodium Chloride Injection, USP  
5% Dextrose and 0.9% Sodium Chloride Injection, USP  
5% Dextrose and 0.33% Sodium Chloride Injection, USP  
NORMODYNE (labetalol HCl) Injection was NOT compatible with 5% Sodium Bicarbonate Injection, USP.

## HOW SUPPLIED

NORMODYNE (labetalol HCl) Injection, 5 mg/ml, is supplied in 20 ml (100 mg) (NDC-0085-0362-07) and 40 ml (200 mg) (NDC-0085-0362-06) multi-dose vials, boxes of 1.  
Store between 2° and 30°C (36° and 86°F). Do not freeze.

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## Clinical Pharmacology of Doxacurium Chloride (BW A938U) in Children

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SARNIER JB, BRANDOM BW, COOK DR, DONG M-L, HORN MC, WOELFEL SK, DAVIS PJ, RUDD GD, FOSTER VJ, McNULTY BF. Clinical pharmacology of doxacurium chloride (BW A938U) in children. *Anesth Analg* 1988;67:303-6.

*The neuromuscular effects of doxacurium were studied in 26 children during halothane-nitrous oxide-oxygen anesthesia. Neuromuscular blockade was measured using electromyographic activity of the adductor pollicis muscle after supramaximal stimulation of the ulnar nerve at 2 Hz for 2 seconds at 10-second intervals. To estimate the cumulative dose-response relation, nine patients received incremental doses of doxacurium (2.5-10 µg/kg); nine*

*patients received 27.5 µg/kg (the estimated ED<sub>95</sub>); eight patients received 50 µg/kg (1.8 × ED<sub>95</sub>). The ED<sub>25</sub>, ED<sub>50</sub>, ED<sub>75</sub>, and ED<sub>95</sub> (estimated from linear regression plots of log dose vs probit of effect) were 11.5, 14.8, 19.0, and 27.3 µg/kg, respectively. Clinical duration (T<sub>25</sub>) was 27.8 ± 10.3 (mean ± SD) minutes at 1 × ED<sub>95</sub> and 50.6 ± 15.6 minutes at 1.8 × ED<sub>95</sub>. Time to recovery of the train-of-four ratio to 0.75 was 63.1 ± 32.9 minutes at 1 × ED<sub>95</sub> and 108.5 ± 25.7 minutes at 1.8 × ED<sub>95</sub>. There were no significant changes in heart rate or mean arterial pressure after bolus administration of any dose of doxacurium.*

Key Words: NEUROMUSCULAR RELAXANTS—doxacurium.

Doxacurium chloride (BW A938U), a new nondepolarizing neuromuscular blocking agent, has a duration of action in adults similar to that of pancuronium and appears to be devoid of cardiovascular effects (1-3). No data are available to describe the pharmacologic effects of doxacurium in children. We determined the dose-response relation, the duration of neuromuscular blockade, and the effects of doxacurium on blood pressure and heart rate in children during halothane-nitrous oxide-oxygen anesthesia.

### Methods

Twenty-six children (ASA status I-II) between 2 and 12 years of age having low-to-moderate risk elective surgical procedures requiring tracheal intubation were studied. Mean age was 6.2 ± 2.8 (SD) years, mean weight 23.1 ± 11.2 kg, mean height 116 ± 17.0 cm, and mean body surface area 0.86 ± 0.25 m<sup>2</sup>. The study was approved by the Human Rights Committee of Children's Hospital of Pittsburgh; informed consent was obtained from a parent. No patient had a history of abnormal response to neuromuscular blocking agents. No patient received aminoglycoside antibiotics or antihistamines within 48 hours of the study. In general, premedication was not given, but 4 of the 26 patients received IM premedication: morphine (100-150 µg/kg) in 3, atropine (8-12.5 µg/kg) in 2, and scopolamine (6 µg/kg) in 1. Hematology profiles, blood chemistries, and urinalyses were measured before and after anesthesia in nine patients.

Anesthesia was induced with nitrous oxide (70%) in oxygen (30%) and halothane (3-4% inspired concentration). An IV catheter was inserted after induc-

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tion of anesthesia and an infusion of 5% dextrose in lactated Ringer's solution was begun. Blood pressure and heart rate were recorded by automated sphygmomanometry (Dinamap). Atropine 10  $\mu\text{g/kg}$  was given IV before tracheal intubation. Tracheal intubation was accomplished without the aid of neuromuscular blocking agents or intravenous or transalaryngeal lidocaine. After intubation the end-tidal halothane concentration was reduced to  $0.8 \pm 0.05\%$ ; nitrous oxide (70%) in oxygen (30%) was continued. Fentanyl (1–3  $\mu\text{g/kg}$ ) was given as needed. End-tidal carbon dioxide was maintained between 4.0–4.5%; body temperature was maintained between 36.5–37.5°C. The ulnar nerve was stimulated supramaximally (pulse width, 0.1 msec) using cutaneous electrodes on the forearm with train-of-four stimuli (2 Hz for 2 seconds at 10-second intervals). The compound electromyogram of the adductor pollicis muscle was recorded using a Puritan-Bennett/Datex monitor. The degree of neuromuscular blockade was described as percentage of control; the height of the first train-of-four response (T1) was compared to the control (initial baseline) electromyogram height. Baseline levels of blood pressure and heart rate were established during a 15-minute period after intubation. End-tidal halothane concentration remained stable during this 15-minute period before administration of doxacurium.

Dose-response relations were established with a cumulative dosing technique (4). Patients in group A ( $n = 9$ ) received an initial bolus of doxacurium (10  $\mu\text{g/kg}$ ) in <5 seconds through a T-connector into a rapid IV infusion. Additional boluses (one to five per patient) of doxacurium (2.5–10  $\mu\text{g/kg}$ ) were given after neuromuscular blockade had stabilized (for at least 1 minute) to achieve at least 75% neuromuscular blockade. Cumulative dosing was accomplished in an average of 15.1 minutes (range 11–23), excluding one patient in whom cumulative dosing required 47 minutes. The calculated  $\text{ED}_{95}$  of doxacurium was administered by IV bolus to patients in group B ( $n = 9$ ). Patients in group C ( $n = 8$ ) received 50  $\mu\text{g/kg}$  ( $1.8 \times \text{ED}_{95}$ ) doxacurium by IV bolus. Mean levels of arterial blood pressure and heart rate were recorded 1, 2, 3, 5, and 10 minutes after administration of the bolus doses of doxacurium.

Residual neuromuscular blockade was antagonized using neostigmine (60  $\mu\text{g/kg}$ ) and atropine (30  $\mu\text{g/kg}$ ) in seven group A patients, four group B patients, and four group C patients. All other patients recovered spontaneously from neuromuscular blockade. All patients were extubated uneventfully in the operating room before transport to the recovery room.

Time in minutes from injection to onset of maximum neuromuscular blockade (the onset time) and

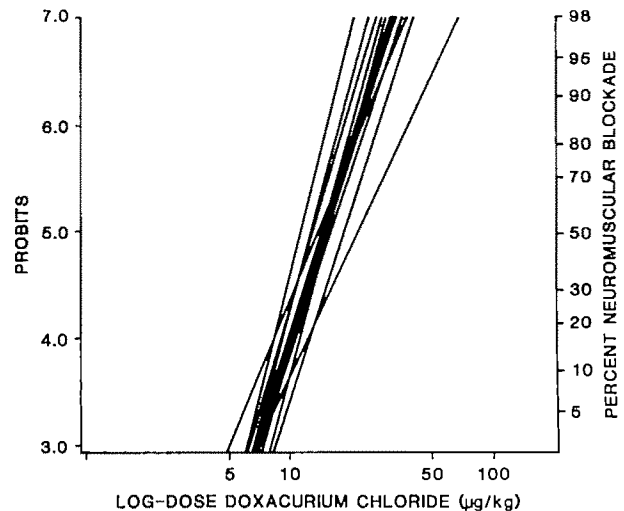


Figure 1. Individual and median (bold face) cumulative dose-response curves for doxacurium in children during halothane nitrous oxide-oxygen anesthesia.

maximum blockade (%) were referenced to the initial electromyogram baseline. Times from administration of doxacurium to 25% (T25) and 75% (T75) spontaneous recovery of neuromuscular transmission were referenced to the final electromyogram baseline attained for each individual patient (5). The time to recovery of the train-of-four ratio to 0.75 and the recovery index (T25–T75) were recorded. Dose data for patients in group A were transformed to log-dose; neuromuscular blockade data were transformed to probits. A log-dose probit response curve was then constructed for each of the group A patients. Least squares regression lines and effective dose estimates were calculated for each patient. Median effective doses were calculated for the group, excluding the patient who required 47 minutes of dosing. The mean maximum neuromuscular blockade in patients in group B and group C was calculated with nontransformed effect data.

All results are reported as mean  $\pm$  SD. The data were analyzed using *t*-tests, Mann-Whitney *U* tests, analysis of variance, and repeated-measures analysis of variance where appropriate. Results were considered statistically significant when  $P \leq 0.05$ .

## Results

There were no differences in the mean age, weight, height, or body surface area between patients in groups A, B, or C. The median values of doxacurium  $\text{ED}_{25}$ , 50, 75, and 95 during halothane-nitrous oxide-oxygen anesthesia were 11.5, 14.8, 19.0, and 27.3



Table 1. Neuromuscular Effects of Doxacurium

	Maximum block(%)	Onset time*(min)	Recovery			
			T25† (min)	T75† (min)	T25-75‡ (min)	T4:1 > 0.75§ (min)
Group A <sup>  </sup>	88 ± 6.6 (79-98) n = 9	— — n = 9	16.3 ± 8.8 (4.5-32.3) n = 9	39.9 ± 11.4 (26.8-57.7) n = 8	25.6 ± 6.3 (15.2-35.6) n = 8	56.0 ± 14.5 (41.5-77.6) n = 5
Group B	91 ± 11.5 (61-100) n = 9	6.7 ± 1.9 (5.5-11.0) n = 9	27.8 ± 10.3 <sup>¶</sup> (16.5-44.7) n = 8	56.7 ± 29.4 (18.0-96.3) n = 8	34.0 ± 16.4 (15.5-57.5) n = 7	63.1 ± 32.9 (39.3-118.0) n = 5
Group C	99 ± 2.2 (96-100) n = 8	5.3 ± 3.2 (1.8-10.3) n = 8	50.6 ± 15.6 <sup>¶</sup> (33.2-79.7) n = 8	72.7 ± 14.3 <sup>¶</sup> (54.0-90.2) n = 5	29.9 ± 12.2 (11.2-41.5) n = 5	108.5 ± 25.7 <sup>¶</sup> (80.7-141.2) n = 4

All values are mean ± sd (range).

\*Onset time is the interval from injection to maximum neuromuscular blockade.

†Time from injection for neuromuscular transmission to recover to 25% of control (T25) or to 75% of control (T75).

‡Recovery index (T25 to T75 interval).

§Time from injection for the train-of-four ratio to spontaneously recover to 0.75.

¶Recovery data are referenced to the final dose of doxacurium.

<sup>||</sup>Significantly different from group A.

n differs between subgroups of patients because patients received neostigmine at variable degrees of recovery. One patient in Group B obtained less than 75% neuromuscular blockade after administration of doxacurium. T25 and T25-75 were therefore not available.

Table 2. Effects of Doxacurium on Blood Pressure and Heart Rate

	Baseline*	Times after doxacurium administration				
		1 minute	2 minutes	3 minutes	5 minutes	10 minutes
Group B						
MAP (mm Hg)	63.2 ± 8.7	64.7 ± 8.2	63.8 ± 8.9	64.1 ± 8.6	62.9 ± 10.4	65.3 ± 11.5
HR (beats/min)	119.8 ± 14.6	119.0 ± 15.0	115.9 ± 13.5	116.3 ± 12.4	114.8 ± 11.8	113.1 ± 12.9
Group C						
MAP (mm Hg)	66.0 ± 9.9	67.1 ± 10.3	65.4 ± 9.2	66.4 ± 7.2	66.4 ± 8.9	71.3 ± 12.5
HR (beats/min)	107.4 ± 15.5	110.4 ± 17.6	109.6 ± 17.2	109.5 ± 15.2	108.8 ± 16.4	108.4 ± 19.1

All Values are mean ± sd.

\*Baseline data were obtained 1 minute before administration of doxacurium. There were no significant differences at any time between or within groups B and C.

μg/kg (Fig. 1). The onset time and recovery data after single bolus injections of 27.5 and 50 μg/kg (groups B and C) are presented in Table 1. Recovery indexes after cumulative dosing (group A) are also presented in Table 1. There was no significant difference between mean levels of maximum blockade in groups A and B. Six of eight patients in group C developed complete blockade; one patient developed 96% blockade and one patient developed 97% blockade. There were no significant changes in blood pressure, heart rate, or cardiac rhythm after an IV bolus of 27.5 μg/kg or 50 μg/kg doxacurium (Table 2). No cutaneous flushing or other adverse events were observed. There were no significant differences between laboratory values before and after anesthesia attributable to administration of doxacurium.

Full recovery of neuromuscular transmission occurred spontaneously in 14 of the 26 patients. Four patients received antagonists for reversal of neuromuscular blockade, at the discretion of the investigator, after recovery of the train-of-four ratio to 0.75.

One patient recovered spontaneously, though train-of-four ratio recovery was not measured because of change in the anesthetic background. T25 was different in all three patient groups. The clinical duration (T25) increased from 27.8 ± 10.3 to 50.6 ± 15.6 minutes when the dose was increased to 50 μg/kg from 27.5. T75 and train-of-four ratio recovery (T4/T1 ≥ 0.75) were significantly prolonged in patients in group C. There was no significant difference in recovery index (T25-T75) between patients in groups A, B, and C. There were no other statistically significant differences between groups. Neostigmine (60 μg/kg) and atropine (30 μg/kg) were given when recovery was between 47 and 98% of final baseline and a T4/T1 ratio of greater than 0.75 followed within 0.16 to 5.7 minutes.

## Discussion

The ED<sub>50</sub> and ED<sub>95</sub> of doxacurium in children during halothane-nitrous oxide-oxygen anesthesia are com-

Table 3. Effective Dosages of Doxacurium in Different Age Groups and Different Anesthetic Backgrounds\*

	Adults (1) narcotic-N <sub>2</sub> O	Adults (2) narcotic-N <sub>2</sub> O	Adults (3) isoflurane	Children† halothane
ED <sub>50</sub>	15.2	13.0	8.6	14.8
ED <sub>95</sub>	25.0	23.0	16.2	27.3

All values in  $\mu\text{g/kg}$ .

\*As reported in the literature (Ref. 1-3) and in the present study†

†Present study.

parable to those reported by other investigators during narcotic-nitrous oxide anesthesia in adults (1,2) (Table 3). This relation between dosage requirements with different age groups and different anesthetic backgrounds occurs with other nondepolarizing muscle relaxants (6-10). Thus, we hypothesize that children will probably require a larger dose ( $\mu\text{g/kg}$ ) of doxacurium than adults to achieve the same degree of neuromuscular blockade during equivalent anesthetic backgrounds. The neuromuscular blocking effects of doxacurium in adults are potentiated by isoflurane (3). Isoflurane potentiation in children has not been reported. These age-related differences may be explained by an increased volume of distribution of doxacurium in children relative to adults. Children may also require higher plasma concentrations of doxacurium than adults to achieve a comparable degree of neuromuscular blockade. Pharmacodynamic and pharmacokinetic studies are necessary to confirm these hypotheses.

At equipotent doses of doxacurium both time to onset of maximum blockade and time to recovery of neuromuscular transmission to T25 are shorter in children during halothane anesthesia than in adults during narcotic anesthesia (1). Shorter onset of blockade is probably related to an increased cardiac output and more rapid distribution of drug to the neuromuscular junction in younger patients. Similar age-related differences in onset of blockade occur with pancuronium (11). More rapid recovery from blockade suggests a higher clearance of the drug in children than in adults. The recovery index (T25-T75) of doxacurium in our study was not significantly different in patients who received 1 or 1.8 times the ED<sub>95</sub>. This is consistent with the absence of a cumulative effect of doxacurium (12). The recovery index in children is about half that reported in adults (13).

Doxacurium had no significant effect on heart rate or blood pressure in children where each patient served as his own control. These measurements were made during a steady state of anesthesia. However, heart rate and blood pressure were not measured in

control patients given the same type of anesthesia for the same length of time for similar surgical procedures but not given doxacurium.

In summary, doxacurium is a long-acting nondepolarizing muscle relaxant devoid of effects on heart rate or blood pressure in healthy children during halothane-nitrous oxide-oxygen anesthesia. Further studies are needed to delineate the response of children in the presence of different types of general anesthesia. In addition, pharmacokinetic studies may explain age-related differences in the neuromuscular effects of this new drug.

Without the assistance of L. Hankins, CRNA, this study could not have progressed as scheduled.

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## Pre- and Postganglionic Sympathetic Nerve Activity during Induced Hypotension with Adenosine or Sodium Nitroprusside in the Anesthetized Rat

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DELLE M, RICKSTEN S-E, DELBRO D. Pre- and postganglionic sympathetic nerve activity during induced hypotension with adenosine or sodium nitroprusside in the anesthetized rat. *Anesth Analg* 1988;67:307-12.

*The aim of this study was to examine the effects of adenosine (AD)-induced hypotension on preganglionic adrenal (aSNA) and postganglionic renal (rSNA) sympathetic nerve activity. rSNA (n = 10) and aSNA (n = 6) were recorded together with mean arterial pressure (MAP) and heart rate (HR) in chloralose-anesthetized, artificially ventilated rats. In each experiment, hypotension was induced by equihypotensive doses of AD (0.03–2.0 mg·kg<sup>-1</sup>·min<sup>-1</sup>) and sodium nitroprusside (SNP) (1–10 µg·kg<sup>-1</sup>·min<sup>-1</sup>). SNP induced a progressive reflex tachycardia and a reflex increase in rSNA to levels 159 ± 35% above control*

*at a MAP reduction of 55% of the normotensive control value. Equipotent doses of AD induced a decrease in HR and significantly less pronounced reflex increase in rSNA. The maximal increase in rSNA with AD was 55 ± 19% at a MAP reduction of 30%. At higher infusions rates of AD, rSNA progressively declined toward the normotensive control values. However, AD elicited a progressive increase in preganglionic aSNA that was not significantly different from the increase seen during SNP infusion. It is concluded that AD-induced hypotension is associated with a suppression of postganglionic sympathetic nerve activity caused by an inhibition of ganglionic neurotransmission.*

**Key Words:** ANESTHETIC TECHNIQUES—hypotensive. SYMPATHETIC NERVOUS SYSTEM—induced hypotension.

Induced arterial hypotension (IAH) is employed during certain operations to facilitate surgery and to decrease blood loss. When accomplished by the commonly used vasodilator, sodium nitroprusside (SNP), IAH unloads arterial baroreceptors, which in turn elicit reflex activation of the sympathoadrenal system as measured by increased levels of plasma catecholamines (1–3). This increase in sympathetic tone also activates the renin-angiotensin system during IAH, partly due to  $\beta$ -adrenergic receptor stimulation (1,4). SNP, when used for IAH, thus causes undesirable side effects, including tachyphylaxis (5–7) and rebound hypertension (4,8,9). Adenosine (AD) and its

related compound, ATP, are endogenous substances with powerful vasodilatory properties that recently have gained an increasing interest as suitable agents for IAH, based on studies in animals (1,10,11–14) and in humans (15–17). AD-like compounds elicit hypotension, which has a more rapid onset and a shorter recovery time than that of SNP and is devoid of tachyphylaxis, tachycardia, and rebound hypertension. Furthermore, neither AD- nor ATP-induced hypotension seems to be associated with changes in plasma renin activity or plasma levels of norepinephrine (2,13). It seems, thus, that exogenously administered AD, in addition to its vasodilatory action, may attenuate the reflex activation of the sympathoadrenal system during IAH considerably. The mechanism behind this latter property of AD may be at least threefold: an inhibitory effect of AD on the release of norepinephrine (18); inhibitory effect of AD on sympathetic ganglionic neurotransmission (19); and an AD-induced central inhibition of the sympathetic outflow. The effects of AD on neurotransmission, using neurophysiologic recording techniques, have been studied only in vitro (19). The purpose of the

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present series of experiments was, therefore, to examine in vivo in what way and to what extent AD affects sympathetic neurotransmission in relation to the hypotensive effect of AD. To this end, we performed direct recordings of pre- and postganglionic sympathetic nerve activity during AD-induced hypotension in chloralose-anesthetized rats.

## Materials and Methods

Male Wistar rats (Møllegaard Breeding Centre, Denmark) weighing 290–380 g were used in this study. Anesthesia was induced with methohexital sodium (Brietal, Eli Lilly Sweden AB, Stockholm) (75 mg/kg body weight). The right jugular vein was cannulated with two PE-50 catheters for drug administration. After a bolus dose of chloralose (50 mg/kg IV) the rats received a continuous infusion of chloralose (20–30 mg·kg<sup>-1</sup>·h<sup>-1</sup>). The trachea was cannulated (PE-250), and the rats were mechanically ventilated with a tidal volume of 1.5–2 ml at a frequency of 75 breaths/min to maintain Paco<sub>2</sub> within normal limits (4.5–5 kPa), which was confirmed by arterial blood samples (120  $\mu$ l) (ABL 20 Radiometer, Copenhagen, Denmark) repeatedly during the experiment. Blood losses due to blood sampling were immediately restored with isotonic saline. Body temperature was kept at about 37°C by means of a rectal thermometer coupled to an infrared heating lamp and a heating pad via a thermostat. Arterial pressure (AP) was measured by a Statham 23 DC pressure transducer connected to a PE-50 catheter in the tail artery; mean arterial pressure (MAP) was obtained by electronic damping of this signal. Heart rate (HR) was measured from the pulse pressure signal by means of a rate meter.

### *Sympathetic Nerve Recordings*

Postganglionic renal sympathetic nerve activity (rSNA) was recorded from one of the renal branches of the left greater splanchnic nerve. Preganglionic sympathetic nerve activity (aSNA) was recorded from an adrenal branch of the left greater splanchnic nerve. The left kidney and adrenal gland were exposed via a retroperitoneal flank incision. The renal or adrenal nerve branch was dissected free from fat and connective tissue for a length of 8–10 mm. The nerve was then placed on a thin bipolar platinum electrode, great care being taken to avoid drying and mechanical damage to the nerve. When optimal recording was achieved, the nerve and the electrode were isolated with silicone rubber (Wacker Sil-gel

604). The flank incision was then closed and the rats were left undisturbed for 2–3 hours before the experimental procedure.

The nerve signal was amplified (Grass 511, Grass Instrument Co., Quincy, MA) and displayed on an oscilloscope (Tektronix Storage Oscilloscope 5115 Beaverton, OR). The signal was also rectified, and the average rectified signal was continuously recorded on a Grass polygraph (model 7) together with AP, MAP, and HR. To verify that sympathetic activity of the adrenal gland nerve recordings was preganglionic in origin, hexamethonium (hexamethonium chloride, Fluka) was injected as a bolus dose (7.5 mg/kg IV). Only those adrenal nerve recordings that responded with an increase in nerve activity to hexamethonium were regarded as preganglionic and were included in the study. In some experiments, hexamethonium was also given when renal sympathetic nerve activity was recorded to confirm the postganglionic activity of the renal nerves.

Nerve activity was recorded for 45–60 minutes after death in all rats as a measure of the level of background "noise," which was subtracted from the mean rectified nerve signal recorded in the living rat.

### *Experimental Procedures*

The same experimental protocol was used in two groups of rats: group A ( $n = 10$ : recordings of MAP, HR, and rSNA (postganglionic); group B ( $n = 6$ ): recordings of MAP, HR, and aSNA (preganglionic). In both groups hypotension was induced first by increasing IV infusion rates of AD (0.03–2.0 mg [0.1–6  $\mu$ mol]·kg<sup>-1</sup>·min<sup>-1</sup>) and second by SNP (1–10  $\mu$ g·kg<sup>-1</sup>·min<sup>-1</sup>) to lower MAP gradually by 70 mm Hg. Hypotension was induced three times with each drug with short recovery periods between each procedure. Fifteen to twenty minutes elapsed between the last AD infusion and the first SNP infusion. At each period of IAH, HR, and aSNA or rSNA activity were measured with every 10-mm Hg decrease from the pre-AD or pre-SNP level of MAP. Mean values of HR, aSNA, and rSNA were calculated from the three periods of IAH for each drug in each experiment. The relationships between MAP decrease (10–70 mm Hg) and changes in aSNA, rSNA, and HR were plotted and the areas under the curves were calculated (product of X and Y axes). HR values from groups A and B were pooled together.

In each experiment dose-response effects of continuous AD infusion of MAP, HR, aSNA, and rSNA were also determined. To reach a steady-state hypotensive level, AD was continuously infused IV during

a 3-minute period at four infusion rates (0.2, 0.5, 1.8, and 5.5  $\mu\text{mol/kg}$  body weight per minute), with a recovery period of 10 minutes between each 3 minute period. Values of MAP and HR from groups A and B were pooled together.

In some of the rats ( $n = 8$ ), an ECG, recorded as limb leads, was registered during both AD and SNP infusions.

Testing for the significance of differences between AD and SNP with respect to effects on aSNA, rSNA, and HR was accomplished by a Student's paired  $t$ -test performed on the areas under the curves. Because the areas under the curves have no physiologic meaning, they are expressed by the numerical values without any units.  $P < 0.05$  was considered statistically significant. Data are expressed as mean values  $\pm$  SEM.

## Results

### rSNA, aSNA, and HR Changes during SNP- or AD-Induced Hypotension

MAP before SNP- and AD-induced hypotension was  $132 \pm 4$  and  $126 \pm 5$  mm Hg, respectively, in group A (NS) and  $130 \pm 5$  and  $130 \pm 7$  mm Hg, respectively, in group B (NS). Corresponding values of HR were  $384 \pm 9$  and  $388 \pm 8$  beats/min in group A (NS) and  $398 \pm 14$  and  $412 \pm 17$  in group B (NS). The mean absolute values of postganglionic rSNA before SNP- and AD-induced hypotension were  $2.2 \pm 0.5$  and  $2.5 \pm 0.8$   $\mu\text{V}$ , respectively, (NS). Corresponding values of preganglionic aSNA were  $0.9 \pm 0.4$  and  $0.9 \pm 0.5$   $\mu\text{V}$  (NS).

The increase in rSNA was clearly less pronounced when AD was used for induction of IAH compared to SNP (Fig. 1). The mean values of the areas under the curves were  $242 \pm 77$  and  $678 \pm 118$  for AD and SNP, respectively ( $P < 0.01$ ). SNP-induced hypotension was associated with a progressive increase in rSNA in all experiments. At a MAP reduction of 70 mm Hg, rSNA was increased by  $159 \pm 35\%$  above the normotensive control value (Fig. 1). AD-induced hypotension was associated with an increase in rSNA at lower infusion rates. The maximal increase in rSNA was  $55 \pm 19\%$  at a MAP reduction of 40 mm Hg. At higher infusion rates, rSNA progressively declined and at a MAP reduction of 70 mm Hg, rSNA was increased by only  $9 \pm 20\%$  above the normotensive control value (Figs. 1, 2A).

Both AD and SNP induced progressive increases in aSNA. The mean values for the areas under the

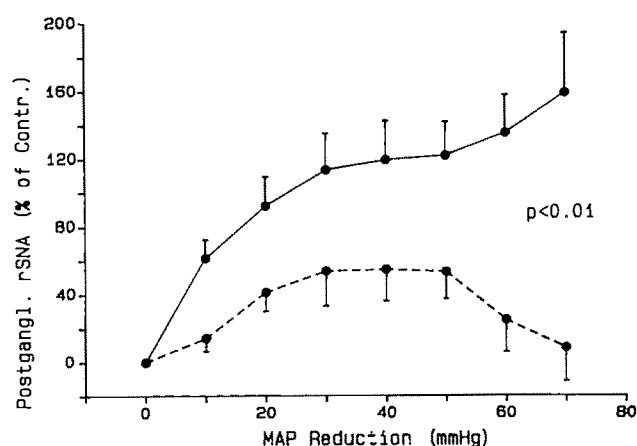


Figure 1. Effects of induced hypotension by sodium nitroprusside (SNP, —) and adenosine (AD, ---) on postganglionic renal sympathetic nerve activity (rSNA). The mean value for the areas under the curves was significantly lower for AD compared to SNP ( $P < 0.01$ ).

curves were  $818 \pm 221$  and  $544 \pm 146$  for AD and SNP, respectively, values not being significantly different ( $P = 0.09$ ) (Figs. 2B and 3).

Effects of SNP and AD on HR are seen in Figure 4. AD induced a clear-cut progressive decrease, whereas SNP induced a progressive increase in HR in all experiments. The mean values of the areas under the curves were  $-132 \pm 40$  and  $130 \pm 29$  ( $P < 0.001$ ) for AD and SNP, respectively (pooled data from groups A and B).

### Dose-Response Effects of Continuous AD Infusion on MAP, HR, rSNA, and aSNA (Fig. 5)

There was a dose-dependent decrease in MAP at the four AD infusion rates (pooled data from groups A and B). HR did not change at the two lower infusion rates (0.2 and 0.5  $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) but decreased at the two higher infusion rates (1.8 and 5.5  $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) (pooled data from groups A and B). At the two lower infusion rates, rSNA as well as aSNA increased ( $24 \pm 11\%$ ,  $50 \pm 11\%$  and  $34 \pm 24\%$ ,  $48 \pm 21\%$ , respectively). At an infusion rate of 1.8  $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , rSNA inhibition started while aSNA further increased. At the highest infusion rate, 5.5  $\mu\text{mol}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , rSNA was only  $7 \pm 20\%$  while aSNA was  $112 \pm 29\%$  above the normotensive control values.

The decrease in HR elicited during AD-induced hypotension was accompanied by an increase in the R-R interval without any signs of arrhythmias on ECG.

## Discussion

The effects on sympathetic neurotransmission in anesthetized rats of the two vasodilatory compounds,

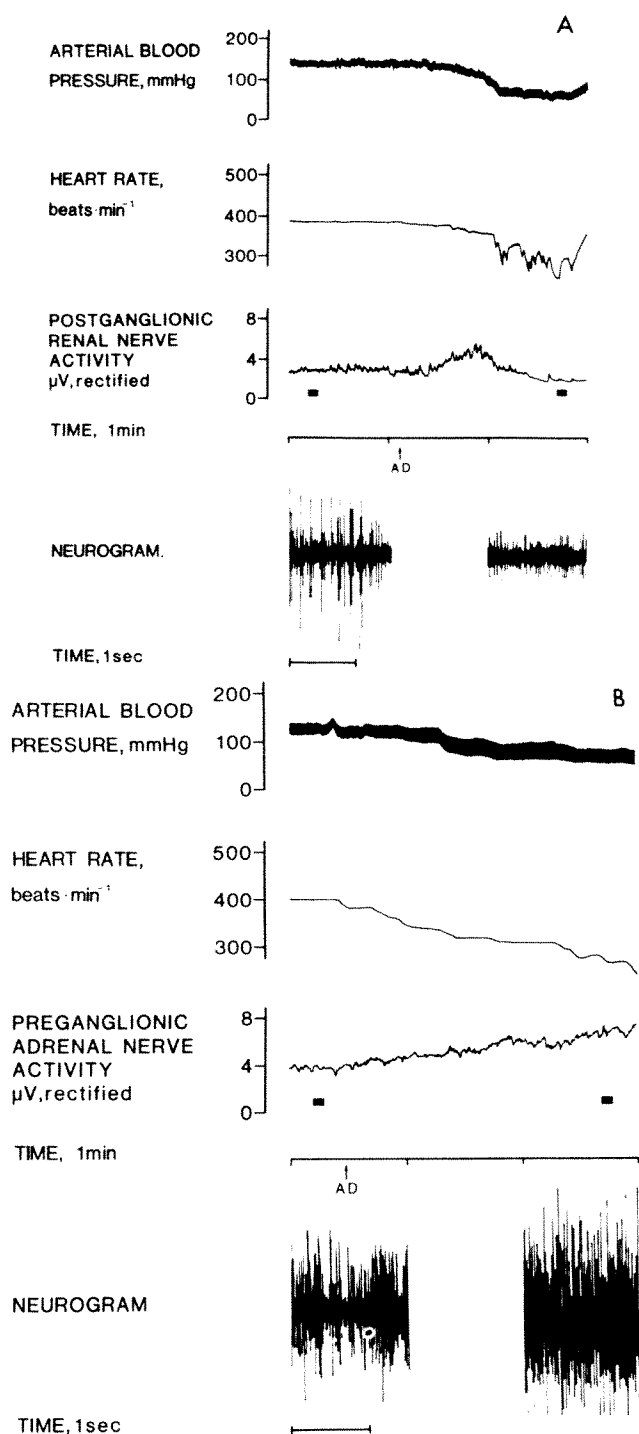


Figure 2. Recordings from two experiments of arterial blood pressure, heart rate, mean rectified postganglionic (A), and preganglionic sympathetic nerve activity (B) during AD-induced hypotension. The sympathetic neurogram during normotension before AD and at the highest AD infusion rate are demonstrated in the lower panel of the figures. At lower infusion rates, postganglionic sympathetic nerve activity (A) increased, whereas at higher infusion rates the activity normalized or even decreased below the normotensive control value, as shown also by a diminished bursting activity in the neurogram. Preganglionic sympathetic nerve activity (B) increased progressively as arterial blood pressure was reduced by AD. Note the increased bursting activity at the highest infusion rate compared with control.

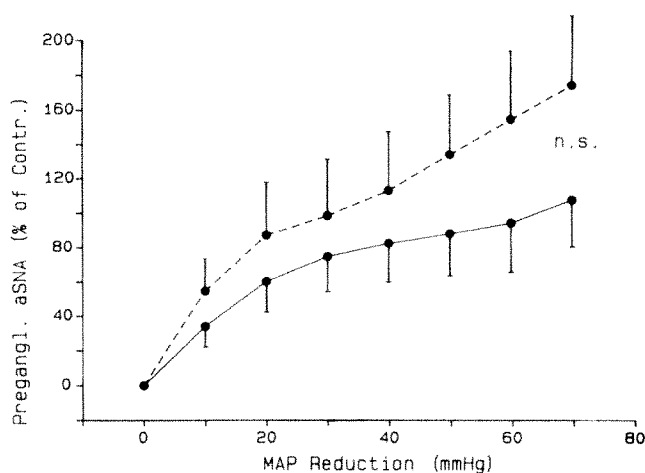


Figure 3. Effects of induced hypotension by sodium nitroprusside (SNP, —) and adenosine (AD, ---) on preganglionic adrenal sympathetic nerve activity (aSNA). The mean values for the areas under the curves did not differ significantly between the groups.

adenosine (AD) and sodium nitroprusside (SNP), were analyzed from recordings of adrenal preganglionic (aSNA) and renal postganglionic (rSNA) sympathetic nerve activity. Theoretically, it would have been more advantageous to measure pre- and postganglionic sympathetic nerve activity in the same sympathetic fiber. However, it is impossible to record from preganglionic renal sympathetic nerves, because these fibers travel in the splanchnic nerve which in turn consists of pre- and postganglionic fibers to many other visceral organs.

SNP-induced hypotension was accompanied by an increase in HR, aSNA, and rSNA, respectively. These findings are in all likelihood an expression of baroreceptor-induced compensatory adjustments of the circulatory apparatus in response to the lowered arterial blood pressure. Interestingly, during AD-induced hypotension, rSNA, after an initial decrease, declined toward normotensive control values, whereas aSNA increased progressively (Figs. 1-3). These data suggest that although the lowered blood pressure reflexly elicits a centrally mediated increase in preganglionic sympathetic nerve activity, AD induces a marked suppression of the postganglionic sympathetic nerve discharge at higher infusion rates. Thus, sympathetic ganglionic neurotransmission is seemingly inhibited by the AD infusion, whereas central reflex pathways are unaffected.

It is known that AD inhibits acetylcholine release presynaptically by interfering with calcium channels, as shown by Alkadhi et al. (19) *in vitro*. In addition, it has been demonstrated that AD may hyperpolarize the postganglionic cell body (20). Both these mechanisms are probably of importance in explaining the



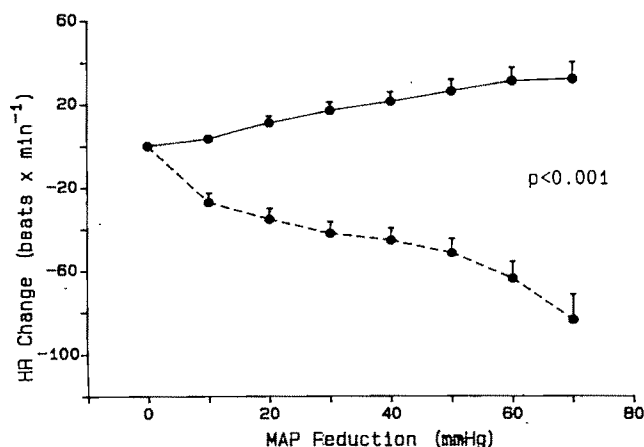


Figure 4. Effects of induced hypotension by sodium nitroprusside (SNP, —) and adenosine (AD, ---) on heart rate (HR). SNP increased, whereas AD decreased HR in all experiments. Mean values presented in the figure represent pooled data from groups A and B. The mean value for the areas under the curves was significantly lower for AD compared with SNP ( $P < 0.001$ ).

inhibition of sympathetic ganglionic transmission induced by AD.

The normalization of rSNA when MAP was reduced by more than 30% at higher AD infusion rates can thus partly explain the observation that AD-induced hypotension has not been associated with increased plasma levels of norepinephrine (13). An inhibitory effect of AD on the release of norepinephrine will of course contribute to explain this finding (18). The rebound hypertension (as well as the tachyphylaxis) usually occurring upon SNP-induced hypotension has been reported to be essentially due to an increased level of plasma renin concentration (1,4). Because sympathetic nerve activity participates in the regulation of renin release from renal juxtaglomerular cells (21), the normalization of rSNA due to inhibition of ganglionic transmission during higher levels of AD infusion may, in part, explain the absence of rebound hypertension when this compound is administered.

AD-induced hypotension was accompanied by a dose-dependent decrease in HR. This phenomenon was most likely due to a direct action of AD on the conductive system of the heart. Thus, it has been reported that AD elicits negative chronotropic and dromotropic effects in several species (22). In the present study, electrocardiographic recordings verified that AD-induced hypotension was associated with an increase in the R-R interval but without any signs of arrhythmias. Furthermore, an inhibitory effect of AD on cardiac sympathetic neuroeffector transmission (23) may also contribute to the bradycardia.

Tachyphylaxis, rebound hypertension, and high cyanide levels are problems associated with use of SNP during anesthesia for controlled hypotension.

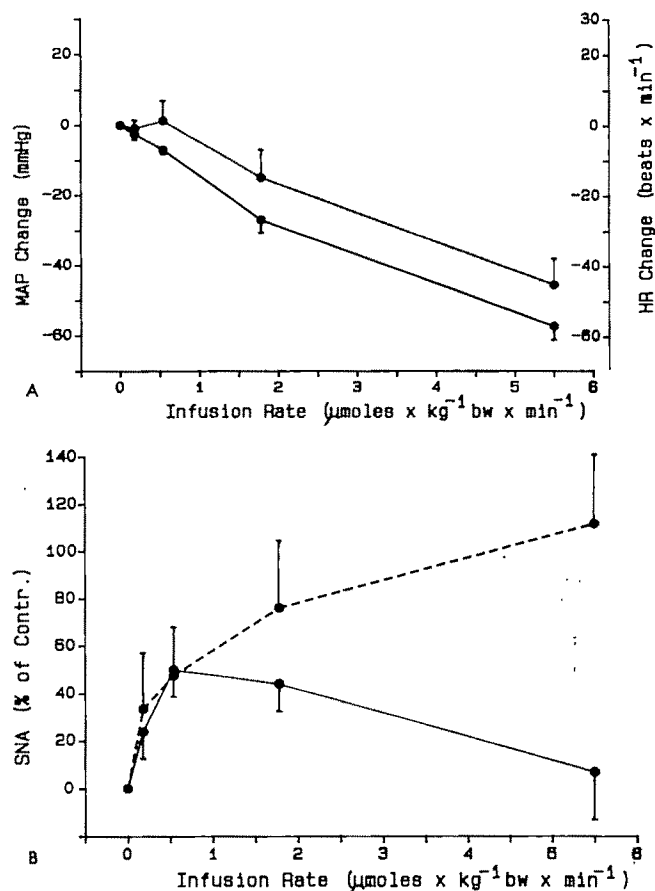


Figure 5. Dose-response effects of adenosine on mean arterial blood pressure (MAP, —) and heart rate (HR, ---) (A) and on postganglionic (—) and preganglionic (---) sympathetic nerve activity (SNA) (B).

These problems have encouraged investigators to study the effects of SNP combined with antihypertensive adjuvant drugs, including  $\beta$ -adrenergic blockers (9), the ganglionic blocking agent trimethaphan (24,25), and the centrally acting  $\alpha$ -adrenoceptor agonist, clonidine (3). These studies have been performed to reduce the amount of SNP required to produce an adequate hypotension and prevent hypertension on discontinuation of SNP. However, with AD as the sole agent for deliberate hypotension in humans and in animals, problems described above have not been reported (see the introduction). Thus, the combination of powerful vasodilating properties and the inhibitory effect on sympathetic ganglionic transmission, as described in this study, makes AD a potentially suitable agent for controlled hypotension not necessarily requiring other adjuvant antihypertensive agents.

We conclude that AD-induced hypotension is associated with a significantly less pronounced reflex increase in rSNA compared to equihypotensive doses of SNP. At higher infusion rates of AD, when MAP is

reduced by more than 30% below control levels, rSNA decreases toward the normotensive control levels, whereas postganglionic rSNA further increases at equipotent doses of SNP. However, aSNA increases continuously and equally during AD- and SNP-induced hypotension. Thus, AD, in addition to its vasodilating properties, exerts a powerful inhibitory effect on sympathetic ganglionic transmission. These findings thus contribute to an understanding of why AD is devoid of tachyphylaxis, tachycardia, and rebound hypertension when used for controlled arterial hypotension.

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## Analgesia and Ventilatory Response to Carbon Dioxide after Intramuscular and Epidural Alfentanil

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PENON C, NEGRE I, ECOFFEY C, GROSS JB, LEVRON J-C, SAMII K. Analgesia and ventilatory response to carbon dioxide after intramuscular and epidural alfentanil. *Anesth Analg* 1988;67:313-7.

*The analgesic and ventilatory depressant effects of epidural and intramuscular alfentanil (15  $\mu\text{g/kg}$ ) were compared in two groups of seven healthy unpremedicated subjects. Fifteen minutes after IM injection, the slope of the ventilatory response to  $\text{CO}_2$  decreased significantly (from  $2.72 \pm 0.34$  to  $1.8 \pm 0.20 \text{ L}\cdot\text{min}^{-1}\cdot\text{mm Hg}^{-1}$ ) while assessment of periosteal analgesia showed no change. After epidural injection, the slope of the ventilatory response to  $\text{CO}_2$  decreased significantly (from  $2.32 \pm 0.42$  to  $1.61 \pm 0.29$ ,*

*$1.51 \pm 0.29$ , and  $1.53 \pm 0.21 \text{ L}\cdot\text{min}^{-1}\cdot\text{mm Hg}^{-1}$ ) at 15, 45, and 90 minutes ( $x \pm \text{SD}$ ,  $P < 0.05$ ), and there was significant periosteal analgesia of the tibia (15 and 30 minutes after injection) and of the radius (30 to 90 minutes after injection). Throughout the study, plasma alfentanil levels were similar after intramuscular and epidural injection. These results suggest that epidural alfentanil induces ventilatory depression due to the rostral spread of the drug rather than to systemic absorption.*

**Key Words:** ANALGESICS—alfentanil. ANESTHETIC TECHNIQUES, EPIDURAL—alfentanil. PAIN—postoperative.

The analgesic effect of epidural morphine is well known (1). Rostral spread of morphine toward the medullary structures causes ventilatory depression attributable to its retention in CSF because of its relatively low lipid solubility.

However, Negre et al. (2) demonstrated both early and prolonged ventilatory depression after epidural administration of fentanyl, which is 100 times as lipid soluble as is morphine. Recently Chauvin et al. (3) studied the pharmacokinetic properties of epidural and intramuscular alfentanil, another lipid-soluble opioid; however, they did not determine its effect on ventilatory control. The aim of this study was to compare the analgesia and the change of ventilatory response to  $\text{CO}_2$  after alfentanil 15  $\mu\text{g/kg}$  given intramuscularly or epidurally.

## Methods

### Patients

The study protocol received institutional approval, and we obtained informed consent from all participants. None had clinical evidence of respiratory, cardiovascular, hepatic, or CNS disorders. Subjects received no medications before the study, were unpremedicated, and had fasted overnight. Two groups were studied: the epidural group comprised seven ASA physical status I males scheduled for minor orthopedic (arthroscopy) or urologic (lithotripsy) procedures. Their mean ( $\pm \text{SD}$ ) age, weight, and height were  $36 \pm 6$  years,  $76 \pm 9$  kg, and  $177 \pm 3$  cm, respectively. The intramuscular group consisted of seven ASA physical status I male volunteers. Their mean ( $\pm \text{SD}$ ) age, weight, and height were  $37 \pm 7$  years,  $75 \pm 9$  kg, and  $177 \pm 5$  cm, respectively.

### Procedure for Intramuscular Injection

The volunteers did not receive an IV infusion; however, we inserted an 18-gauge venous catheter to obtain blood samples for measurement of plasma alfentanil concentrations. After baseline measure-

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ments, we injected alfentanil 15  $\mu\text{g/kg}$  into the quadriceps muscle.

### *Procedure for Epidural Injection*

We began an infusion of Ringer's lactate solution (3  $\text{ml}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ ) through an 18-gauge venous catheter and administered atropine 0.5 mg IV. The ECG was continuously displayed on an electrocardioscope and arterial blood pressure was measured by a sphygmomanometer cuff. With patients in the sitting position, we used a 17-gauge Tuohy needle to insert an epidural catheter at the L3-L4 interspace and advanced the catheter until the 10-cm mark was at skin level. After an aspiration test, we injected, 1 hour before the start of the study, 2 ml lidocaine 2% with epinephrine 1:200,000 to rule out an accidental intravascular or dural puncture. We then turned the patient supine with a 45° head-up tilt and injected alfentanil (15  $\mu\text{g/kg}$ ) in 10 ml saline. After the study, we injected the epidural catheter with local anesthetics to provide surgical anesthesia. All patients obtained effective anesthesia for surgery.

### *Clinical Effects*

We evaluated analgesia before and every 15 minutes after alfentanil injection as follows: 1) cutaneous analgesia, defined as the dermatome level of subjective change in sensation to ice and to pinprick; 2) maximum tolerance to periosteal pressure over the anterior surface of the tibia and the distal end of the radius as determined by the average of three readings made with a calibrated, spring-loaded rod (4). The subject's tolerance to periosteal pressure was expressed as percentage change from baseline value before alfentanil injection. We also recorded side effects such as pruritus, nausea, and drowsiness.

### *Ventilatory Measurements*

For all subjects, we performed CO<sub>2</sub> stimulation test on the day before the procedure to familiarize them with the experiment. Results of this test were not included in the data. Tidal volume (VT), respiratory rate (RR), and minute ventilation ( $\dot{V}_E$ ) were recorded with the subjects breathing room air and during CO<sub>2</sub> rebreathing, with a mouthpiece and a nose clip, through a pneumotachograph (Fleisch No. 2) and Rudolph nonrebreathing valve. Instrument dead space was 70 ml. The resistance to inspiratory and

expiratory flows were 2.4 and 3.6  $\text{cm H}_2\text{O}\cdot\text{L}^{-1}\cdot\text{sec}^{-1}$ , respectively, at a flow of 1 L/sec. Ventilatory response to CO<sub>2</sub> was assessed by rebreathing for 4 to 5 minutes from a 7-L spirometer filled with a mixture of 7% CO<sub>2</sub> in O<sub>2</sub>. Volume was measured by electronically integrating the flow signal obtained from a Godart 17212 differential pressure transducer (Bilthoven Holland) connected to a pneumotachograph, previously calibrated with a 1-L syringe of air. End-tidal CO<sub>2</sub> tension ( $P_{ET\text{CO}_2}$ ) was measured with a Godart capnograph (Bilthoven Holland) calibrated with 5%, 7%, and 9% mixtures of CO<sub>2</sub> in O<sub>2</sub>, verified to be within 1% using Scholander microanalysis. Pneumotachograph and capnograph outputs were interfaced to a CBM SX64 computer with an analog-to-digital converter (5). After converting ventilatory variables to BTPS, linear regression equations were computed from  $\dot{V}_E$  and  $P_{ET\text{CO}_2}$  for each CO<sub>2</sub> challenge curve. The correlation coefficients were ranged from 0.94 to 0.98. We performed duplicate CO<sub>2</sub> response curve measurements before as well as 15, 45, 90, and 120 minutes after intramuscular and epidural alfentanil injections.

### *Plasma Alfentanil Analysis*

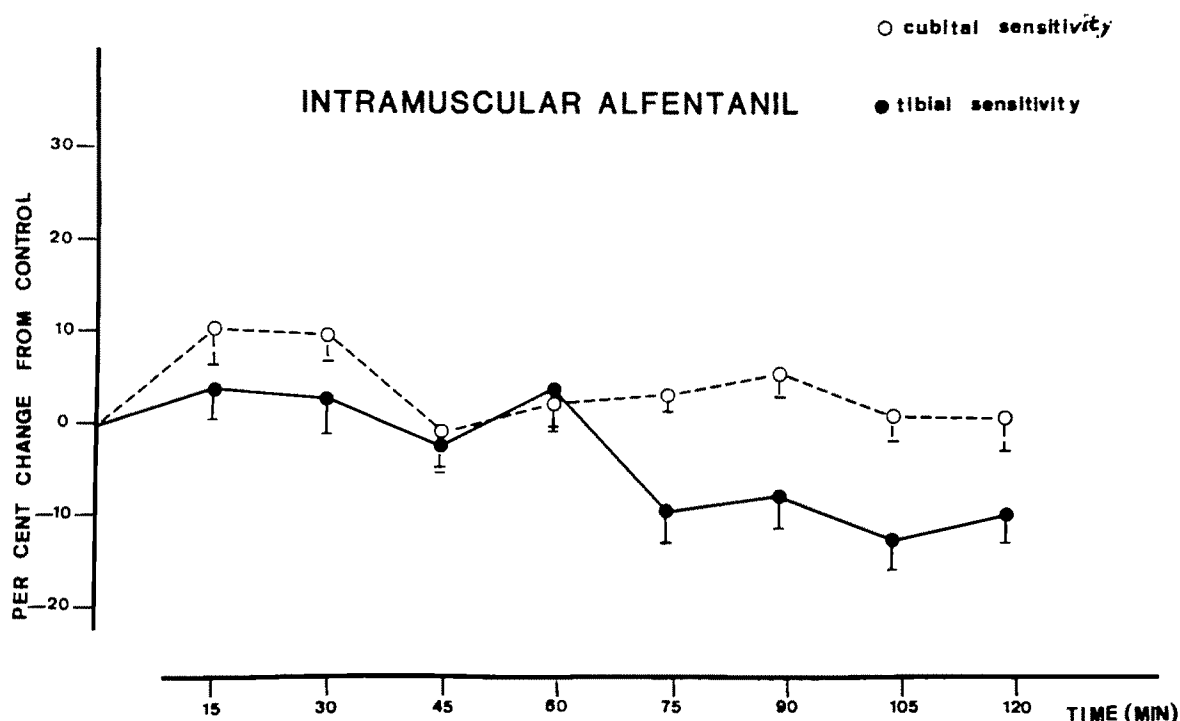
Plasma alfentanil levels were assayed from venous blood samples taken 15, 45, 90, and 120 minutes after the injection of alfentanil, just before each CO<sub>2</sub> rebreathing test. Plasma was separated by centrifugation at -4°C, stored at -20°C and was assayed in duplicate by radioimmunoassay. Alfentanil was measured in our laboratory with a minimum detectable level of 0.1 ng/ml and a coefficient of variation of <3% (6).

### *Statistical Analysis*

Differences between respiratory and analgesia variables at each time interval and baseline values were tested using one-way analysis of variance followed by the use of the Dunnett test for multiple comparisons. Differences between the two groups were tested with the use of the *t*-test for unpaired data. Differences between the two groups in plasma levels of alfentanil were tested using the nonparametric test of Mann-Whitney. *P* < 0.05 was considered statistically significant.

### *Results*

The two groups were not significantly different concerning age, weight, height, resting respiratory variables, and baseline tolerance to periosteal pressure.



### Intramuscular Group

Apnea never occurred. Transient drowsiness was observed 15 minutes after injection in all patients. Periosteal pain threshold did not change (Fig. 1). Ventilatory variables are summarized in Table 1. Resting  $\dot{V}_E$ , RR, and  $P_{ETCO_2}$  values did not change. The  $\dot{V}_E/P_{ETCO_2}$  slope decreased significantly 15 minutes after alfentanil.

Figure 1. Maximum tolerance to periosteal pressure after intramuscular alfentanil. Mean values  $\pm$  SEM.

### Epidural Group

No side effects occurred. We could not determine a precise cutaneous level of analgesia; however, we observed significant periosteal analgesia in the tibia (15 and 30 minutes after injection) and in the radius

Table 1. Respiratory Variables and Plasma Alfentanil Values before and after Intramuscular and Epidural Alfentanil (15  $\mu$ g/kg)

	Control	Minutes after alfentanil administration			
		15	45	90	120
Resting $P_{ETCO_2}$ * (mmHg)					
IM	39.3 $\pm$ 1.0†	39.9 $\pm$ 1.2	39.9 $\pm$ 1.1	39.6 $\pm$ 1.2	39.1 $\pm$ 1.4
Epidural	38.8 $\pm$ 1.2	39.5 $\pm$ 1.5	39.3 $\pm$ 0.8	39.9 $\pm$ 1.2	38.3 $\pm$ 0.9
Resting RR (breaths/min)					
IM	15.2 $\pm$ 0.8	14.2 $\pm$ 0.6	14.0 $\pm$ 0.6	15.1 $\pm$ 0.4	16.1 $\pm$ 0.6
Epidural	11.9 $\pm$ 0.8	13.1 $\pm$ 1.0	13.4 $\pm$ 1.0	14.2 $\pm$ 2.2	13.9 $\pm$ 1.3
Resting $\dot{V}_E$ (L/min)					
IM	11.5 $\pm$ 1.3	9.5 $\pm$ 0.8	9.5 $\pm$ 0.9	9.3 $\pm$ 0.5	10.3 $\pm$ 0.9
Epidural	12.3 $\pm$ 1.0	10.6 $\pm$ 0.8	10.1 $\pm$ 1.1	11.5 $\pm$ 1.4	11.4 $\pm$ 1.3
Slope $\dot{V}_E/P_{ETCO_2}$ (L·m <sup>-1</sup> ·mm Hg <sup>-1</sup> )					
IM	2.72 $\pm$ 0.34	1.81 $\pm$ 0.20‡	2.15 $\pm$ 0.35	2.34 $\pm$ 0.45	2.58 $\pm$ 0.27
Epidural	2.32 $\pm$ 0.42	1.61 $\pm$ 0.29‡	1.51 $\pm$ 0.29‡	1.53 $\pm$ 0.21‡	1.92 $\pm$ 0.34
Plasma alfentanil (ng/ml)					
IM		23.9 $\pm$ 3.2	20.7 $\pm$ 2.9	16.9 $\pm$ 3.0	14.3 $\pm$ 2.1
Epidural		15.9 $\pm$ 2.3	16.3 $\pm$ 2.6	22.2 $\pm$ 2.6	17.8 $\pm$ 1.4

\* $P_{ETCO_2}$ , end-tidal  $CO_2$  tension; RR, respiratory rate;  $\dot{V}_E$ , minute ventilation.

†Mean values  $\pm$  SEM.

‡ $p < 0.05$  from control value.

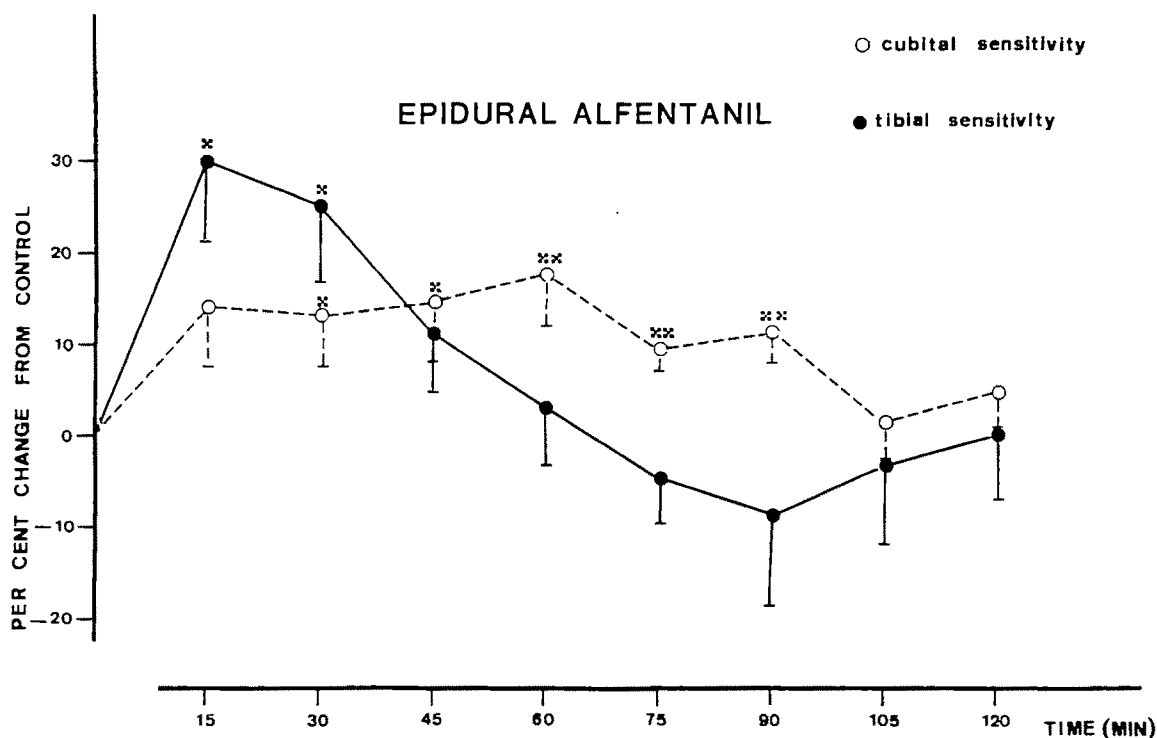


Figure 2. Maximum tolerance to periosteal pressure after epidural alfentanil. Mean values  $\pm$  SEM. \* $P < 0.05$ , \*\* $P < 0.01$  versus control.

(30 to 90 minutes after injection) (Fig. 2). Ventilatory variables are summarized in Table 1. Epidural alfentanil did not change resting RR,  $\dot{V}_E$ , and  $P_{ETCO_2}$ . The  $\dot{V}_E/P_{ETCO_2}$  slope decreased significantly from baseline value 15, 45, and 90 minutes after epidural alfentanil. Throughout the study, plasma alfentanil levels were similar in the epidural and in the intramuscular groups.

## Discussion

Despite similar plasma levels of alfentanil after intramuscular and epidural administration, we found that IM alfentanil produced respiratory depression that lasted <30 minutes after injection, whereas epidural alfentanil produced significant ventilatory depression until 90 minutes after injection. The respiratory depression observed at 15 minutes in the intramuscular group is probably an effect related to blood concentration of the drug. There is no available information in the literature on the relationship between alfentanil plasma levels and the occurrence of respiratory depression. However, the fact that the peak plasma level of alfentanil also occurred 15 minutes after intramuscular administration, as previously reported

by Chauvin et al. (3), strongly suggests that this early respiratory depression is related to blood concentration of the drug.

Absorption into the systemic circulation might also explain the respiratory depression observed 15 minutes after epidural injection of alfentanil. However, several facts suggest that the prolonged ventilatory depression 45 and 90 minutes after injection is probably related to rostral spread of the narcotic. First, despite similar plasma alfentanil levels, respiratory depression was of shorter duration after IM injection. In addition, the ventilatory depression in the epidural group was associated with the spread of periosteal analgesia in a rostral direction, which suggests a rostral spread of alfentanil in the neuraxis as previously reported by Bromage et al. after epidural morphine injection (4,7). This spread may have occurred either in the CSF or via direct perimedullary vascular channels (1). Late depression of the slope of the ventilatory response to  $CO_2$  after epidural opioid administration has been previously reported with both morphine (which has a low lipid solubility) (7) and fentanyl (which is a highly lipid-soluble opioid) (2). This refutes the hypothesis that, unlike morphine, lipid-soluble opioids easily cross the dura and are rapidly absorbed by the spinal cord, inducing segmental analgesia without the side effects associated with rostral migration. In conclusion, epidural alfentanil induces a prolonged depression of the control of ventilation. It is therefore



necessary to closely monitor patients receiving epidural alfentanil.

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## Recurrent Herpes Simplex Virus Labialis and the Use of Epidural Morphine in Obstetric Patients

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CRONE L-AL, CONLY JM, CLARK KM, CRICHLOW AC, WARDELL GC, ZBITNEW A, REA LM, CRONK SL, ANDERSON CM, TAN LK, ALBRITTON WL. Recurrent herpes simplex virus labialis and the use of epidural morphine in obstetric patients. *Anesth Analg* 1988;67:318-23.

*A retrospective study of sequential obstetric patients delivering at University Hospital and receiving epidural anesthesia was conducted to determine if a suggested association exists between the recurrence of oral herpes simplex lesions and the use of epidural morphine. In a retrospective study of 291 patients, 13 of 134 (9.7%) receiving epidural morphine developed recurrent oral herpes lesions in contrast to 1 of 157 (0.6%) not receiving the drug ( $P < 0.001$ ). In a prospective hospital-based study of 729 consecutive obstetric patients, 146 patients received epidural opioids (morphine, fentanyl, or both) and 583 did not. Recurrent HSVL lesions*

*occurred in 13 of 140 (9.3%) patients given epidural morphine but in only 6 of 583 (1.0%) not given epidural opioids ( $P < 0.001$ ). Three of the 13 patients with HSVL received both epidural morphine and fentanyl and 10 received only epidural morphine. Because of the small numbers of patients receiving only fentanyl, no relation between HSVL reactivation and epidural fentanyl could be established. In patients having cesarean sections, the association of recurrent HSVL and the use of epidural morphine was significant ( $P = 0.04$ ), suggesting cesarean delivery was not a confounder. A hitherto undescribed triggering agent, epidural morphine, appears to be associated with reactivation of HSVL in obstetric patients in the postpartum period.*

Key Words: ANESTHESIA, obstetric. ANESTHETIC TECHNIQUES, EPIDURAL—morphine. INFECTION—herpes simplex.

Herpes simplex virus labialis (HSV-L), commonly known as a cold sore or fever blister, is a manifestation of the reactivation of latent HSV-1 infection in humans (1). Recurrent genital infection is the most common form of herpes (HSV-2) occurring during gestation (2), but epidemiologic studies of HSV-1 in pregnancy are rare. Reactivation of HSV-L can be triggered by exposure to ultraviolet light, fever, immunosuppression, or trauma, with lesions usually

appearing along the distribution of the third division of the trigeminal nerve.

In 1985, a possible increase in the frequency of recurrent HSV-L was observed in obstetrical patients who had received epidural morphine for postoperative analgesia after cesarean delivery in our hospital. To appropriately analyze this clinical observation, a retrospective and prospective study was designed. Epidemiologic data relating to the incidence of HSV-L and reactivation rates in pregnant women in our geographic area were also examined.

### Materials and Methods

#### *Retrospective Study*

Hospital records of sequential obstetrical patients who had received epidural anesthesia for delivery at our institution were examined during an 8 month period between January and August 1985. The data

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**Table 1.** Retrospective Study of Parturients Receiving Epidural Anesthetic

Administration of epidural morphine	Oral HSVL (%)			Facial pruritus (%)		
	Present	Absent	Total	Present	Absent	Total
Yes	13 (9.7)*	121 (90.3)	134	52 (46.3)†	72 (53.7)	134
No	1 (0.6)	156 (99.4)	157	3 (1.9)	154 (98.1)	157
Total	14 (4.8)	277 (95.2)	291	55 (22.3)	226 (77.7)	291

\* $P < 0.001$ ; relative risk = 16.† $P < 0.001$ ; relative risk = 24.

analyzed included incidence of cold sores (HSV), incidence of facial pruritus, type of delivery (vaginal or cesarean), age, parity, and administration of epidural morphine. Occurrence of typical vesicular lesions on the lips, with or without virological confirmation, and occurrence of pruritus was retrieved from the nursing progress notes and the epidural narcotic monitoring record. Epidural drugs used for analgesia in labor or for surgical anesthesia during cesarean section varied, depending on preferences of individual anesthesiologists, and included carbonated lidocaine and bupivacaine 0.25% or 0.5%, administered through an epidural catheter. For postoperative analgesia after cesarean section, a single dose (4 or 5 mg) of preservative-free morphine (Epimorph) was given. Epidural morphine was the only epidural opioid used in our institution during this study.

### Prospective Study

Because of limitations of our retrospective data, statistical analysis could not take into account several potential confounders such as age, parity, type of delivery with its associated stress, trauma, and history of recurrent HSV. We therefore designed a prospective study. Our objective was to determine whether the frequency of reactivation of HSV is greater after the use of epidural morphine in the early postpartum period. Following approval by the institutional ethics committee, parturients delivering between January and August 1986 entered the study with informed consent. Information relating to the history of previous cold sores was recorded on a study data collection form, and patients were observed daily for 5 days after delivery by an infection control nurse for evidence of reactivation.

Clinical verification of diagnosis of HSV was attempted by viral isolation in patients who developed oral lesions. Culturettes (Cepti-Seal-Abbott Labs) were used to collect the specimens, which were inoculated into Vero-cell cultures and, when the cell culture showed cytopathic effects, the virus was identified by indirect immunofluorescence using

monoclonal HSV-I and HSV-II antibody (IAF Production INC).

Preservative-free local anesthetics, administered epidurally for pain relief during labor and for surgical anesthesia in cesarean sections, varied depending on the preferences of the individual anesthesiologists. Preservative-free epidural fentanyl (50–75  $\mu$ g) was administered to patients during labor or cesarean section when incomplete sensory blockade occurred despite appropriate doses of local anesthetics. For postoperative pain relief after cesarean delivery, a single dose (4 or 5 mg) of preservative-free epidural morphine sulfate (Epimorph) was used. Drugs were injected through a nylon epidural catheter. No other epidural opioids were used in this study. Severe facial pruritus was treated postoperatively with intermittent IV injections of naloxone 0.08 to 0.1 mg.

### Community Study

An additional aspect of the prospective study comprised a community study conducted to determine the incidence of HSV and the frequency of reactivation of HSV in our geographic area in obstetrical patients. Following approval by the institutional ethics committee and with the cooperation of the Community Health Unit, Saskatoon, Saskatchewan, demographic data were collected from women who had delivered in our city from January to August 1986. All postpartum women were visited within 10 days of delivery for follow-up by the Community Health Unit. During this routine visit, a questionnaire was completed by the patient. Information obtained included age, parity, hospital of delivery, type of delivery (vaginal or cesarean), past history of cold sores, and occurrence of cold sores within 5 days of delivery. Confidentiality was maintained by the lack of any personal identifiers associated with the form.

Statistical analysis of all three studies was performed using Pearson  $\chi^2$ , Yates corrected  $\chi^2$ , and the Mantel-Haenszel  $\chi^2$  test using the BMDP computer analysis programs (California).  $P < 0.05$  was considered statistically significant. For relatively small num-



Table 2. Prospective Study—Incidence of HSVL and Pruritus in Obstetric Patients

	Type of anesthesia (%)				Type of delivery (%)	
	None	Epidural	General anesthesia	Total	Vaginal	Cesarean
Number of Patients	332 (45.5)	348 (47.7)	49 (6.7)	729 (100)	524 (71.9)	205 (28.1)
Oral HSVL	2 (0.5)	17* (4.9)	0 —	19 (2.6)	5 (1.0)	14‡ (6.8)
Pruritus	8 (2.1)	123† (35.3)	3 (6.1)	131 (18)	13 (2.5)	118§ (57.6)

\* $P < 0.001$ , relative risk = 9.3.† $P < 0.001$ , relative risk = 16.8.‡ $P < 0.001$ , relative risk = 7.2.§ $P < 0.001$ , relative risk = 23.|| $P = 0.025$ .¶ $P < 0.001$ , relative risk = 12.# $P = 0.04$ , relative risk = 6.0.\*\* $P < 0.001$ , relative risk = 7.4.

bers of patients in certain subgroups of the prospective study, Fisher's exact test was used.

## Results

### Retrospective Study

Medical records of 291 sequential parturients who delivered at University Hospital between January 1 and August 31, 1985, and who had received epidural anesthesia were analyzed (Table 1). The mean age was  $26.2 \pm 0.3$  years (SEM) with a parity of  $0.9 \pm 0.1$  (SEM). Of these patients, 152 were delivered vaginally and 139 by cesarean section. Epidural morphine was administered for postoperative analgesia to 134 of the 139 in the cesarean group; none of the patients who delivered vaginally received epidural morphine. Other epidural narcotics were not being used in our institution during this study. Recurrent HSVL lesions developed in 13 of the 134 patients (9.7%) given epidural morphine in the early postpartum period, but in only 1 of 157 patients (0.6%) who did not receive epidural morphine. Pruritus occurred in 62 patients (46.3%) given Epidorm and in 3 of the patients (1.9%) not having epidural morphine. A significant association ( $P < 0.001$ ) between the use of epidural morphine and reactivation of HSVL lesions was noted, with a relative risk of 16. The association of pruritus and the use of epidural morphine was similarly significant ( $P < 0.001$ ).

### Prospective Study

From January to August 1986, we studied 729 consecutive obstetric patients delivering at University Hos-

pital (Table 2). The mean age of the parturients was  $27.5 \pm 0.2$  years (SEM) with a parity of  $2.1 \pm 0.1$  (SEM). Of the 729 women, 710 (97%) were assigned to ASA physical status 1 or 2.

HSVL lesions developed in 19 of the 729 (2.6%) patients in the postpartum period, with 14 of the 19 patients giving a history of previous cold sores. Epidural anesthesia had been administered to 17 of the 19 patients, in 14 for cesarean sections and in 3 for vaginal delivery. Two patients having vaginal deliveries without epidural anesthesia developed HSVL lesions. Of the 729 patients, 364 (49.9%) gave a history of previous HSVL, which correlates with previously reported epidemiologic studies (1).

Among the 146 patients who received epidural opioids, recurrent HSVL lesions developed in 13 (9%), compared to 6 of 583 (1%) who did not receive epidural opioids ( $P < 0.001$ ), with a relative risk of 8.7. Facial pruritus occurred in 77% of women receiving epidural opioids but in only 3% of the nonopioid group ( $P < 0.001$ ), with a relative risk of 25.0. Thirty-five patients received epidural fentanyl, with or without epidural morphine. None of the patients having vaginal deliveries and epidural fentanyl ( $n = 6$ ) developed HSVL, but cold sores occurred in 3 of 29 patients receiving both epidural fentanyl and morphine during cesarean section.

Of the 205 women delivered by cesarean section, 14 (6.8%) developed HSVL lesions postpartum (Table 2). All of these 14 patients had epidural anesthesia and 13 of the 14 received epidural morphine for postoperative pain relief. Three of the 13 patients developing HSVL received both epidural fentanyl and morphine and 10 received only epidural morphine. HSVL did not occur in any patients receiving general anesthesia. Pruritus occurred in 118 of 205

Table 2. (continued)

Type of delivery and anesthesia (%)				Type of delivery and receiving epidural opiates (Total = 146)	
Vaginal— no anesthesia	Vaginal + epidural	Cesarean + epidural	Cesarean + general anesthesia	Vaginal + epidural + fentanyl	Cesarean + epidural + morphine ± fentanyl
332 (45.5)	192 (26.3)	156 (21.4)	49 (6.7)	6 —	140 —
2 (0.6)	3 (1.6)	14    (9.0)	0 —	0 —	13# (9.3)
5 (1.5)	8 (4.2)	115¶ (73.7)	3 (6.1)	2	111** (79.3)

Table 3. Cesarean Sections and Postoperative Analgesia

	HSV L	No HSV L	Total
Epidural morphine	13*	127	140
Parenteral narcotic	1	64	65
Total	14	191	205

\* $P = 0.04$ .

(58%) patients in the group delivered by cesarean section and in 111 of 140 (79.3%) patients given epidural morphine. The association of pruritus and epidural morphine was statistically significant ( $P < 0.001$ ), with a relative risk of 7.4. The association of pruritus and epidural fentanyl could not be established as most patients having fentanyl also received morphine. Pruritus was documented in 13 of the 19 cases (68.4%) with reactivated HSVL. The association of epidural morphine and HSVL in the subgroup of those having cesarean sections and receiving epidural morphine was significant ( $P = 0.04$ , Fisher's exact test), with a relative risk of 6.0 (Table 3). Those not receiving epidural morphine included 49 patients having a general anaesthetic and 16 with epidural anaesthesia.

Variables including age, parity, number of cold sores during this pregnancy, and past history of HSVL were analyzed (Table 4). There were no differences comparing patients having vaginal deliveries to those having cesarean sections. When comparing patients receiving epidural opioids to those who did not, no significant difference between the groups was observed. Grouped according to the type of anesthetic administered, there was no significant difference between the groups receiving general anesthesia, epidural anesthesia, or no anesthesia. Lesions varied in severity, from single or multiple vesicles on the vermilion border, to multiple confluent perioral lesions, extending to the labial commissure and apex of the nose, and to completely cover the alae nasi. Recurrent HSVL lesions observed in this study usu-

ally occurred on the second or third postpartum day and many were anecdotally reported as being the most severe reactivation the patient had ever experienced. A few patients having their second or third cesarean delivery and not receiving epidural morphine in the past, stated that they only experienced reactivation after administration of epidural morphine.

No primary HSV infections were observed, nor was there any recognition of maternal to neonatal transmission in the form of primary neonatal HSV infection. Samples for asymptomatic oral viral shedding and serological titres were not performed in this study. Of the 19 patients in whom HSVL reactivation developed, swabs and cultures were obtained from 16; the results were positive for HSV-1 in 8. No isolates of oral HSV-2 were reported.

Bupivacaine 0.25% without epinephrine was the most frequently used local anesthetic for pain of labor and carbonated lidocaine hydrochloride with 1:200,000 epinephrine was the most frequently used agent for cesarean delivery. Sixteen of the 19 patients (84%) with HSVL had carbonated lidocaine. Intravenous naloxone was administered within the first 24 hours postoperatively for facial pruritus in 8 of the 19 cases of HSVL (43%).

### Community Study

From February to August 1986, information was collected from 990 postpartum patients who delivered their infants in Saskatoon (Table 5). The frequency of reactivation of HSVL within 5 days of delivery was significantly greater ( $P < 0.05$ ) among those who underwent cesarean section (9.6%) than in those undergoing vaginal delivery (4%). During this study it was noted that anesthetists in all three community hospitals were routinely administering epidural morphine for postoperative pain relief after

**Table 4.** Comparability of Obstetric Patient Groups with Respect to Type of Delivery and Anesthesia—Prospective Study

Type of anesthesia	Cesarean			Vaginal	
	GA	Epidural	EM	Epidural	No epidural
Number of patients	49	156	140	192	332
Age (mean)	28.8	28.7	28.8	25.9	27.8
Parity (mean)	2.2	2.8	2.2	1.6	2.4
Number of cold sores* (mean)	0.2	0.1	0.2	0.2	0.4
History of HSVL (%)	52	43	51	44	53

\*Number of cold sores during current pregnancy.

Abbreviation: EM, epidural morphine

No significant difference between groups of patients (Pearson  $\chi^2$ , Yates corrected  $\chi^2$ , Mantel-Haenszel  $\chi^2$ ).**Table 5.** Community Study—Demographics of Postpartum Patients

Type of delivery	Oral HSVL within 5 days of delivery (%)			History of HSVL in lifetime (%)		
	Present	Absent	Total	Present	Absent	Total
Vaginal	33 (4)	800 (96)	833	367 (44.1)	466 (55.9)	833
Cesarean	15 (9.6)*	142 (90.4)	157	83 (52.9)†	74 (47.1)	157
Total	48	942	990	450	540	990

\* $P < 0.05$ .† $P = 0.05$ .

cesarean delivery. The community rate of 4% reactivation of HSVL after vaginal delivery is higher than the 2.6% documented at our hospital during this study (Table 2). The prior lifetime history of HSVL, unrelated to pregnancy, in this community population was 44%, similar to the incidence in the general population (1).

## Discussion

Administration of epidural morphine for postoperative analgesia after cesarean delivery has gained widespread popularity and has been used at our institution for several years. Common side effects include pruritus in the distribution of the trigeminal nerve, urinary retention, nausea and, less frequently, delayed respiratory depression (3).

Our observation corroborates the clinical impression that there is reactivation of HSVL lesions in obstetric patients after the use of epidural morphine (4,5). Gieraerts et al. (5) have reported a higher incidence of HSVL reactivation in the patients having cesarean section and receiving epidural morphine than in our study. A similar association of reactivation of HSVL has been suggested with the use of intrathecal narcotics in pediatric patients (6,7). Our study suggests an association between the use of epidural morphine, the occurrence of facial pruritus, and the reactivation of HSVL in the obstetric popu-

lation. No association between the use of epidural fentanyl and reactivation of HSVL can be suggested from this study because of the small numbers receiving only fentanyl.

The mechanism of reactivation is not known. The skin trigger and ganglion trigger theories (8) are both plausible and, in the former, reactivation of HSVL could be explained by the pruritus and ensuing scratching. It is improbable that altered immunologic response, as suggested by Gieraerts (5), is involved as a reactivation mechanism. Obstetrical patients having cesarean sections and not having epidural morphine do not reactivate HSVL. The mechanism producing pruritus along the trigeminal nerve distribution is unknown although evidence seems to support the case for a central-naloxone-reversible component (9). The addition of epinephrine to solutions used in the epidural space intensifies the pruritus (10).

We propose that the mechanism responsible for the facial pruritus may be related to the reactivation of HSVL, perhaps associated with endogenous opioid activity within the spinal nucleus of the trigeminal nerve, secondary to rostral spread of the epidural morphine (11). There is also speculation as to whether this could involve lumbosacral ganglia. The incidence of genital HSV reactivation was not determined in our study, nor was the frequency of asymptomatic oral viral shedding. Arvin et al. (12) have suggested that genital viral shedding does not predict the infant's risk of exposure to HSV at delivery.



Because both HSV-1 and HSV-2 can be cultured from oral lesions, and the risks to the newborn are equal for both types of HSV (13), further studies on the epidemiology of oral viral shedding in the parturient are warranted.

A hitherto undescribed triggering agent, epidural morphine, appears to be associated with pruritus and reactivation of HSVL in obstetric patients in the immediate postpartum period. No differences in patient populations could be identified that might otherwise account for this observation, including the stress of cesarean delivery itself. However, other unlikely but potential confounding variables such as the addition of epinephrine to the local anesthetic solution, administration of intravenous naloxone, the local anesthetic solution itself, and use of other epidural narcotics may have contributed. Additional controlled prospective clinical and experimental animal studies are needed to confirm the association and determine the mechanism of reactivation of HSV in association with epidural morphine in obstetric and nonobstetric populations. There is presently no data to suggest that morphine given by any other parenteral route reactivates HSVL in any population. A randomized prospective study has been initiated at our institution to address these various confounders in obstetric patients.

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## A Double-Blind Study of the Respiratory Effects of Nalbuphine Hydrochloride in Spontaneously Breathing Anesthetized Patients

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O'CONNOR SA, WILKINSON DJ. A double-blind study of the respiratory effects of nalbuphine hydrochloride in spontaneously breathing anesthetized patients. *Anesth Analg* 1988; 67:324-8.

*Nalbuphine hydrochloride 0.2 mg/kg was compared with meperidine 0.5 mg/kg in a double-blind study in 20 patients undergoing elective inguinal hernia repair while breathing spontaneously under general anesthesia. The respiratory effects of the two drugs studied were continuously and accurately recorded with a wet wedge spirometer throughout the procedure.*

*The acute respiratory effects of these analgesic drugs could therefore be assessed. The measurements recorded before any surgical stimulation showed that both nalbuphine and meperidine produce a similar degree of respiratory depression. These results are at variance with earlier studies that drew conclusions from measurements that were neither continuous nor accurate. Nalbuphine was found to be a satisfactory analgesic adjuvant in this anesthetic technique.*

**Key Words:** ANALGESICS—meperidine, nalbuphine.

Nalbuphine hydrochloride (Nubain, du Pont) is a semisynthetic narcotic agonist/antagonist analgesic of the phenanthrene series. Animal studies suggest it is a potent  $\kappa$ -opiate receptor agonist and a  $\mu$ -opiate receptor antagonist. It should therefore be capable of providing analgesia with minimal respiratory depression, have little significant action at the  $\sigma$ -opiate receptors, and hence cause minimal dysphoria (1).

Nalbuphine has been used extensively in anesthetic practice outside the United Kingdom, and it was found to be an acceptable premedicant providing sedation and analgesia without dysphoria or severe respiratory depression (2,3).

Intraoperatively, the use of nalbuphine has been limited primarily to patients in whom respirations were controlled (4,5). There are, however, a few reports of the use of the drug in patients breathing spontaneously (4,6).

From these studies it appears that nalbuphine is a good analgesic with possible advantages over other opiates in that it may produce minimal respiratory

depression. We designed this study therefore to evaluate the respiratory effects of nalbuphine compared with meperidine in patients breathing spontaneously under general anesthesia. A previously published study (7) showed that meperidine 0.5 mg/kg provided a satisfactory opioid adjuvant in a balanced anesthetic technique. It was decided to compare this dose with the manufacturer's recommended dosage of nalbuphine 0.2 mg/kg.

### Methods

#### *Patients*

Twenty patients undergoing elective surgery for the repair of inguinal hernia were investigated in a double-blind manner. All patients were seen preoperatively to assess their fitness and, if ASA grades 1 or 2, to obtain informed consent for this study, which had been approved by the local ethics committee.

Patients were premedicated with diazepam 0.15 mg/kg orally 2 hours preoperatively. Anesthesia was induced with a sleep dose of thiopental preceded by metoclopramide 10 mg and atropine 0.6 mg IV. Succinylcholine 1 mg/kg was then given, the larynx sprayed with 4% lidocaine, and a cuffed oral tracheal tube passed. The lungs were then ventilated manually until spontaneous respiration resumed. The patient breathed a gas mixture of 30% oxygen in nitrous

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oxide, with 1% halothane added, at a fresh gas flow of 100 ml·kg<sup>-1</sup>·min<sup>-1</sup> from a Mapleson A (Magill) circuit throughout the procedure.

Tidal volume was obtained from the output of a wet wedge spirometer (8). Carbon dioxide concentration was recorded continuously using a Gould Mark IV capnograph sampling gas at 200 ml/min from the proximal end of the tracheal tube, this method of respiratory measurement during anesthesia having been previously validated in other studies (7).

Within approximately 10 minutes of induction, a steady state of respiration under anesthesia was achieved. We defined this as a steady respiratory frequency and tidal volume and a stable end-tidal carbon dioxide concentration.

Once a 3-minute record of the respiratory variables had been obtained during the steady state of respiration the intravenous infusion of analgesic was commenced. The patients were randomly allocated to one of two groups. One group received 0.5 mg/kg meperidine, the other 0.2 mg/kg nalbuphine, both made up to 30 ml, which was given over 3 minutes using a Sage syringe pump, model 355. A further 7 minutes elapsed after this infusion before the surgeons were allowed to prepare the operative site and start surgery.

Recordings were continued throughout the procedure until the halothane was switched off at the end of the operation, at which time the patient was extubated and transferred to the recovery room and given 4 L of oxygen by face mask. The recovery nurse recorded the time at which the patient was able to obey a simple command and also assessed the general condition of the patient at 5 and 10 minutes after obeying their first command.

Calculations were made from the continuous record of tidal volume to give minute volume by summation of each individual tidal expiration in the chosen minute. Respiratory frequency was derived from the same record. End-tidal carbon dioxide concentration was calculated from the continuous trace of tidal carbon dioxide concentration. Calculations from the continuous traces were made at 14 time points; during steady state, every minute for 10 minutes from the start of the analgesic infusion, at incision, and when the halothane was switched off at the end of the surgical procedure. Postoperatively, the patients were given opiate analgesics if they were in pain, the time of such administration being noted. Every patient was seen on the day after their surgery by one of the investigators and any side effects were noted.

Table 1. Demographic Data of Patients Studied

	Nalbuphine	Meperidine
No. of patients	10	10
Age (years)		
Mean	51	45
SD	13.1	17.3
Range	26-67	23-68
Weight (kg)		
Mean	73	81
SD	10.5	6.4
Range	52-92	69-85
ASA classification		
I	7	9
II	3	1
Number of patients with type of inguinal hernia		
Direct	6	6
Indirect	4	4
Number of patients in each classification of difficulty of operation		
Easy	8	7
Moderate	1	2
Difficult	1	1

### Statistics

Assessment of the respiratory depressive effects of the analgesic infusions used was made solely from the data obtained before surgical stimulation. Analysis of variance was performed on the calculated values of respiratory frequency, minute volume, and end tidal carbon dioxide concentration at the 14 specific time points. Mean timings such as duration of anesthesia were also analyzed in this way.

The time from the start of the analgesic infusion to the first postoperative request for analgesia was analyzed using a Mann-Whitney U test as the data were not normally distributed. This latter test was also used to analyze the data relating to the condition of the patient in recovery. The data recorded by the investigators regarding side effects was analyzed by a  $\chi^2$  test and a 50% probability test.

### Results

Table 1 shows the demographic data of the 20 male patients studied, by treatment, the ASA classification of the patients, together with the type of inguinal hernia repaired, and the degree of difficulty of the operation as assessed by the surgeon. The patients in each treatment group were evenly distributed and were therefore comparable.

Tables 2, 3, and 4 show the means and standard errors of the means for respiratory frequency, minute volume, and end-tidal carbon dioxide concentration



Table 2. Respiratory Frequency (breaths/min) During Steady State of Respiration, Start of Analgesic Infusion (I), and at Minute Intervals up to I + 10 and also at Incision and When Halothane Was Switched Off at the End of the Operative Procedure

	Nalbuphine mean (SE)	Meperidine mean (SE)
Steady state	27 (1.4)	26 (1.4)
Start of infusion (I)	27 (1.5)	26 (1.5)
I + 1 min	24 (1.8)	26 (1.8)
I + 2 min	19 (2.2)	23 (2.3)
I + 3 min	17 (2.3)	18 (2.3)
I + 4 min	17 (1.9)	17 (2.0)
I + 5 min	17 (1.8)	16 (1.9)
I + 6 min	16 (1.6)	16 (1.7)
I + 7 min	17 (1.7)	15 (1.9)
I + 8 min	17 (2.2)	15 (2.2)
I + 9 min	14 (2.0)	18 (1.8)
I + 10 min	16 (2.5)	18 (2.0)
Incision	18 (1.9)	17 (1.9)
Halothane off	23 (2.2)	28 (2.2)

Table 3. Minute Volume (L) During Steady State of Respiration, at the Start of Analgesic Infusion (I), and at Minute Intervals up to I + 10 and Also at Incision and When Halothane Was Switched Off at the End of the Operative Procedure

	Nalbuphine mean (SE)	Meperidine mean (SE)
Steady state	6.7 (0.43)	6.1 (0.43)
Start of infusion	6.5 (0.47)	5.9 (0.47)
I + 1 min	4.8 (0.70)	6.1 (0.70)
I + 2 min	3.4 (0.72)	5.1 (0.72)
I + 3 min	3.0 (0.64)	3.6 (0.64)
I + 4 min	3.5 (0.54)	3.2 (0.57)
I + 5 min	3.9 (0.47)	3.5 (0.50)
I + 6 min	4.1 (0.41)	3.5 (0.43)
I + 7 min	4.4 (0.41)	3.4 (0.45)
I + 8 min	4.0 (0.52)	3.6 (0.52)
I + 9 min	3.5 (0.59)	4.4 (0.52)
I + 10 min	3.6 (0.93)	4.3 (0.72)
Incision	6.9 (0.75)	6.0 (0.75)
Halothane off	6.5 (0.56)	6.4 (0.56)

at the steady rate of respiration under anesthesia, the start of the analgesic infusion (I), at minute intervals up to I + 10 minutes, at incision, and at the end of the operative procedure when the halothane was switched off.

Figures 1, 2, and 3 show the median values for respiratory frequency, minute volume, and end-tidal carbon dioxide concentration at the 14 time points described above.

Respiratory frequency and minute volume decreased in both treatment groups within 2 minutes of the start of the analgesic infusion, indicative of respiratory depression of a similar order. End-tidal carbon

Table 4. End-Tidal Carbon Dioxide During Steady State of Respiration, at the Start of Analgesic Infusion (I), and at Minute Intervals up to I + 10 and Also at Incision and When Halothane Was Switched Off at the End of the Operative Procedure

	Nalbuphine mean (SE)	Meperidine mean (SE)
Steady state	5.7 (0.23)	5.9 (0.23)
Start of infusion (I)	5.8 (0.24)	5.8 (0.24)
I + 1 min	5.9 (0.26)	5.8 (0.26)
I + 2 min	6.3 (0.27)	5.8 (0.26)
I + 3 min	6.1 (0.43)	6.3 (0.38)
I + 4 min	6.7 (0.41)	6.3 (0.41)
I + 5 min	6.8 (0.28)	6.7 (0.30)
I + 6 min	7.1 (0.30)	6.8 (0.32)
I + 7 min	7.1 (0.31)	6.9 (0.34)
I + 8 min	7.4 (0.34)	6.8 (0.34)
I + 9 min	7.2 (0.48)	7.1 (0.43)
I + 10 min	7.2 (0.48)	7.1 (0.46)
Incision	6.9 (0.32)	7.0 (0.34)
Halothane off	6.3 (0.27)	6.0 (0.27)

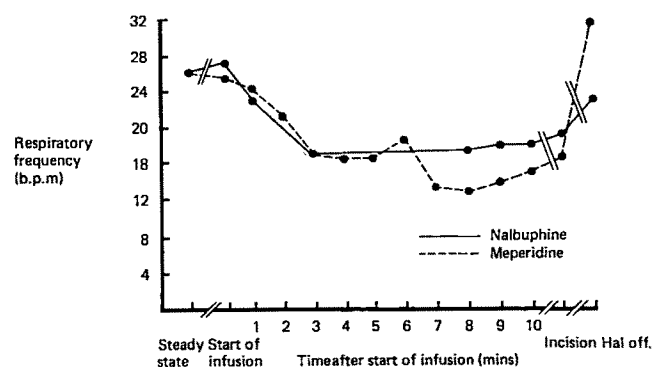


Figure 1. Median values of respiratory frequency in patients receiving nalbuphine and meperidine.

dioxide concentration increased slowly and by 6 minutes after the start of the infusion the values indicated some degree of respiratory depression in both treatment groups. However, at no time for any of these pulmonary indexes was there a statistically significant difference between the two treatment groups.

For each treatment group the mean time from premedication to induction of anesthesia, from induction of anesthesia to halothane being switched off at the end of the operation, for the operative procedure, from halothane being switched off to the patient obeying a simple command, and from the start of the infusion of analgesic to the first request for analgesia postoperatively are shown in Table 5. There were no statistically significant differences between treatment groups for these times despite the apparent large difference in mean time to the request for

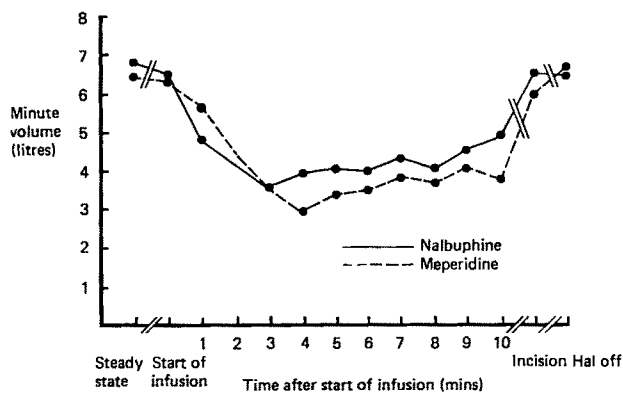


Figure 2. Median values of minute volume in patients receiving nalbuphine and meperidine.

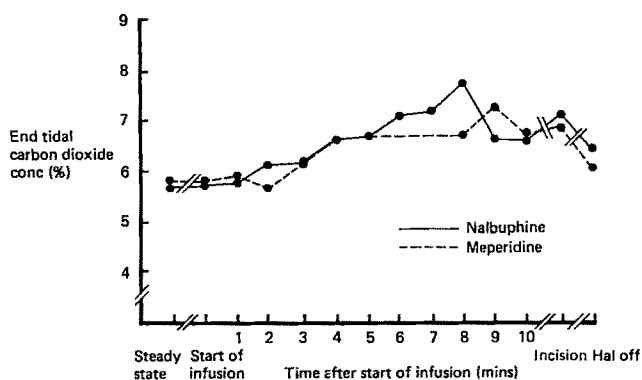


Figure 3. Median values of end tidal carbon dioxide concentration in patients receiving nalbuphine and meperidine.

postoperative analgesia which in the nalbuphine group was 1368 minutes and in the meperidine group was 289 minutes. One patient in the nalbuphine group required no analgesia at all postoperative. The condition of the patient in the recovery room 5 and 10 minutes after obeying a simple command as assessed by the recovery nurse on a four-point scale is shown in Table 6.

There were more patients considered to be in pain in the nalbuphine group than in the meperidine group, but this did not reach statistical significance.

All but two patients, one in each treatment group, experienced some side effects postoperatively. Many of these side effects are probably unrelated to the analgesic treatments, but they are listed in Table 7. There was no statistically significant difference between the two groups studied with respect to these side effects.

## Discussion

There are few reports on the use of nalbuphine in patients breathing spontaneously under anesthesia.

Table 5. Relevant Times Through the Anesthetic and Surgical Procedures

	Nalbuphine mean (SE)	Meperidine mean (SE)
Time from premedication to induction of anesthesia (min)	100 (16.2)	112 (15.3)
Time from induction of anesthesia to halothane switched off (min)	68 (5.9)	77 (5.9)
Length of operative procedure (min)	36 (4.3)	41 (4.3)
Time from halothane switched off to patient obeying simple command (min)	20 (2.4)	21 (2.4)
Time from start of analgesic infusion to first postoperative request for analgesia (min)	1368	289

Table 6. Patient Condition in Recovery Room as Assessed by the Recovery Room Nurse 5 and 10 Minutes After Patients Were Able to Obey a Simple Command

	5 min		10 min	
	Nalbuphine	Meperidine	Nalbuphine	Meperidine
Total number of patients	9	10	10	9
Sleepy and comfortable	6	8	6	5
Fully awake and comfortable	0	1	0	3
Sleepy and in pain	3	1	3	1
Fully awake and in pain	0	0	1	0

We have found that the effects produced by nalbuphine 0.2 mg/kg are very similar to those produced by 0.5 mg/kg meperidine in terms of the condition of the patient both intra- and postoperatively. Furthermore our double-blind study shows that nalbuphine is a satisfactory adjunct to a balanced anesthetic technique in this dosage when patients are breathing halothane spontaneously. This is in agreement with Klepper et al. (6) who, in their open study compared equianalgesic doses of nalbuphine and morphine in patients breathing spontaneously under halothane anesthesia. Their findings, based on recordings of tidal volume from an electronic respirometer and total ventilation from a dry gas meter on a nonstandard anesthetic circuit, were that in conventional dosages nalbuphine and morphine produced identical respiratory depression.

Our results are at variance with the often quoted work of Magruder et al. (4). Their study, which included only six patients breathing spontaneously during anesthesia, utilized respiratory frequency as the sole index of depression of respiration. No conclusions should be drawn from such a small population.

Table 7. Numbers of Patients Experiencing Side Effects in the First 24 hr Postoperatively

	Nalbuphine	Meperidine
Drowsiness	5	8
Nausea	2	4
Vomiting	0	1
Sweating	1	4
Headache	1	2
Insomnia	2	1
Sore throat	1	1
Abdominal discomfort	2	2
None	1	1

Magruder et al. (4) and another study (5) have assessed the respiratory depression induced by nalbuphine given either as a premedicant or intraoperatively solely by an assessment of postoperative respiratory status in patients electively ventilated during operative procedure. No accurate or continuous measurements of respiration were made after nalbuphine administration. No conclusions on the acute respiratory effects of nalbuphine can be made from these studies.

Fragen and Caldwell. (2) attempted to measure the acute respiratory effects of intravenous nalbuphine. Unfortunately their technique of volume measurement, an inferential anemometer coupled to a close-fitting face mask, is grossly inaccurate and this inaccuracy is compounded by the variation in anxiety experienced by awake patients in the stressful environment of the operating theatre. No valid conclusions should be drawn from respiratory measurements made in such circumstances.

Our methodology permits a continuous and accurate assessment of the respiratory effects of nalbuphine during general anesthesia and clearly demonstrates the acute depression in respiration after nalbuphine administration.

The side effects seen postoperatively show some interesting features. Because nalbuphine is a  $\kappa$ -opoid receptor agonist, one would have expected greater sedation from those patients receiving nalbuphine. This was not the case for reasons that are unclear.

The anesthetic sequence was satisfactory for all patients and their postoperative recoveries were un-

eventful. Clinically, both treatments produced adequate analgesia, and there was no difference in postoperative analgesic requirements. All patients experienced some degree of respiratory depression from the analgesic infusion after benzodiazepine premedication. The effects of nalbuphine administered in this manner after an opiate premedication remain unknown.

In conclusion, we believe that nalbuphine and meperidine in the doses of 0.2 and 0.5 mg/kg, respectively, used in the anesthetic sequence described, exhibit similar respiratory depressive effects intraoperatively.

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## Fentanyl Blood Concentration–Analgesic Response Relationship in the Treatment of Postoperative Pain

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GOURLAY GK, KOWALSKI SR, PLUMMER JL, COUSINS MJ, ARMSTRONG PJ. Fentanyl blood concentration–analgesic response relationship in the treatment of postoperative pain. *Anesth Analg* 1988;67:329–37.

*The inter- and intrasubject variability in blood concentration–analgesic response relationship for fentanyl were investigated using the technique of patient-controlled analgesia (PCA) in 30 consenting patients scheduled for surgical procedures involving an abdominal incision (15 upper and 15 lower abdominal incisions). All patients had a thio-pental, nitrous oxide/oxygen, pancuronium anesthetic with 200 µg fentanyl intraoperatively. Postoperative pain relief was provided with fentanyl from a Janssen On-Demand Analgesic Computer (ODAC) set to provide a basal infusion rate of 20 µg/hr, a bolus "demand" dose of 20 µg, and a lockout period of 5 minutes. Frequent blood samples were collected immediately before patients demanded doses, and these were taken as an estimate of the minimum effective concentration (MEC). A mean of 22 samples (range 12 to 45) were collected per patient over a mean study duration of 50 hours (range 24 to 72). The patients required larger hourly fentanyl doses in the first 6-hour period ( $83.9 \pm$*

*30.1 µg/hr) than in any other 6-hour period (mean values varied from 37.3 to 63 µg/hr). The mean ( $\pm$  SD) hourly fentanyl dose rate and total cumulative dose were  $55.8 \pm 22$  µg/hr (range 28.8 to 136 µg/hr) and  $2739 \pm 1191$  µg (range 900 to 6260 µg), respectively. The mean ( $\pm$  SD) MEC was  $0.63 \pm 0.25$  ng/ml (five-fold range from 0.23 to 1.18) and the mean intrapatient coefficient of variation in MEC was 30.2% (range 16 to 46%). The MEC values remained relatively constant in all patients over the 48-hour study period. The small intrapatient variation in MEC over the study period supports a relationship between blood fentanyl concentration and the extent of pain relief. Therefore, the large fluctuations in the hourly fentanyl dose rate do not accurately reflect the relatively constant blood concentration–analgesic effect relationship. These data emphasize the care necessary in the use of mean hourly fentanyl dose requirements as derived from PCA infusions as indexes of pharmacodynamic effects, especially pain relief. A similar situation may exist for the other opioids used in PCA infusion pumps. Psychological factors were found to have some predictive value for MEC and maintenance dose requirements.*

**Key Words:** PAIN—postoperative. ANALGESICS—fentanyl.

A relation between blood or plasma drug opioid concentration and analgesic effect in the treatment of postoperative pain has been demonstrated for meperidine (1,2), morphine (3), methadone (4,5), and ketobemidone (6). These studies (1–6) have led to the concept of a minimum effective concentration (MEC) for opioids for relief of postoperative pain. This concept proposes that consistent and constant pain relief should be observed if the blood opioid concen-

tration is maintained in excess of the MEC value, whereas pain will return if the blood opioid concentration decreases below the MEC.

A common feature of the above studies was the relatively small intrapatient variation in MEC for each opioid in the treatment of postoperative pain. In contrast, there was a large interpatient variation in the blood or plasma concentration of opioid required to achieve adequate pain relief. For example, with morphine (3) there was a five-fold interpatient variation in the MEC, with meperidine (1,2), an eight-fold variation, and with methadone the variation was approximately three-fold (4,5). Factors such as the depression status of the patient, psychological profile, and sociocultural behavior patterns related to

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"models" of pain behavior to which the patient had been exposed as a child have been suggested as contributing to the wide interpatient variation in MEC (7).

Fentanyl is a synthetic opioid of high potency used widely in anesthesia but rarely in postoperative pain control because of the short duration of pain relief after conventional parenteral doses. However, the pharmacodynamic effects of fentanyl are rapidly observed after intravenous administration because of its relatively high lipophilicity. Therefore, fentanyl is used in patient-controlled analgesia (PCA) pumps for control of postoperative pain.

Although blood or plasma fentanyl concentration-pharmacodynamic response relationships have been demonstrated for loss of consciousness ( $34 \pm 7$  ng/ml [8]), EEG changes ( $6.9 \pm 1.5$  ng/ml [9]), respiratory depression ( $1-5$  ng/ml [10,12]), suppression of cardiovascular responses associated with tracheal intubation ( $102 \pm 50$  ng/ml [13]) and extubation ( $3$  ng/ml [14,15]), and prevention of intraoperative increases in blood pressure associated with surgical stimulation ( $<15$  ng/ml, [15]), the blood concentrations associated with postoperative pain relief have not been well characterized. Lehmann et al. (16) suggested that a plasma concentration of approximately  $1$  ng/ml would be necessary for postoperative pain relief. However, these results were based on studies in which relatively few blood samples (mean of eight per patient) were collected over a brief time period (5-10 hours).

The technique of PCA using an on-demand analgesic computer (ODAC) pump was used to examine the following aims: 1) whether any relationship exists between blood fentanyl concentration and analgesic effect, 2) to characterize the inter- and inpatient variation in MEC by collecting frequent blood samples, 3) to examine whether there was any temporal relationship in the MEC values over the 48-hour study period and, 4) to predict, preoperatively, both the mean hourly fentanyl input rate and fentanyl MEC from psychological traits.

Several studies have reported a correlation between assessed preoperative psychological traits (determined by questionnaire) and postoperative opioid requirement or levels of pain assessed by pain scores (17-22).

## Methods

### *Patient Selection*

Thirty patients undergoing abdominal surgery involving either an upper ( $n = 15$ ) or lower ( $n = 15$ )

abdominal incision consented to be included in the study. Patients with significantly impaired renal or hepatic function, chronic respiratory illness, documented hypersensitivity to opioids, or a history of drug abuse were excluded. The study was approved by the Drug and Therapeutics Advisory Committee and the Clinical Investigation Committee of our institution, and patients were free to withdraw from the study.

### *Preliminary Investigations*

Before surgery, each patient was instructed in the use of the ODAC apparatus and completed the following psychological questionnaires:

1. Beck Depression Inventory, a self-rating scale of depression (23).
2. Illness Behaviour Questionnaire, which scored seven traits useful in the examination of the impact of the surgical event on the patient (24). The seven traits were (a) general hypochondriasis, (b) disease conviction, (c) psychological compared to somatic perception of the illness, (d) affective inhibition, (e) affective disturbance, (f) denial, and, (g) irritability.
3. The Eysenck Personality Questionnaire (25), which examines extroversion/introversion, neuroticism, and social conformity (i.e., the tendency for the patient to answer the questions to please the investigator rather than truthfully).

### *Premedication and Anesthetic Management*

Each patient was premedicated with  $10$  mg diazepam orally 2 hours before surgery. Anesthesia, induced with thiopental ( $4$  to  $5$  mg/kg), was followed by succinylcholine to facilitate endotracheal intubation. All patients were then given  $200$   $\mu$ g fentanyl IV and anesthesia was thereafter maintained with nitrous oxide/oxygen (2:1) supplemented with pancuronium for muscle relaxation. Enflurane ( $0.5-1\%$ ) was added to the anesthetic if the patient exhibited clinical signs of light anesthesia. Reversal of neuromuscular blockade was achieved with neostigmine and atropine.

Before induction of anesthesia, an intravenous catheter fitted with a double three-way stopcock was inserted via the antecubital fossa and advanced so that the tip of the catheter was in the vicinity of the subclavian vein. This catheter was used throughout the study for the collection of blood samples. A separate peripheral intravenous line fitted with a

one-way valve was inserted in the contralateral arm and used to infuse fentanyl via the ODAC pump.

### *Postoperative Pain Control and Measurement of MEC*

On arrival in the recovery ward, the patient was connected to the ODAC machine with the variables initially set as follows:

Basal infusion rate: 20  $\mu\text{g/hr}$ ,  
Bolus demand dose: 20  $\mu\text{g}$ ,  
Maximum hourly dose: 180  $\mu\text{g}$ ,  
Lockout period between doses: 5 minutes.

Before patient-initiated demands, 5-ml blood samples were collected into heparinized tubes and stored at  $-20^{\circ}\text{C}$  until analyzed. Samples were generally analyzed within a week of a patient completing the study and stability experiments revealed that fentanyl was stable for at least 2 months when stored at  $-20^{\circ}\text{C}$ . The blood concentration of fentanyl was determined by gas-liquid chromatography with nitrogen-phosphorus detection as previously described (26). The blood fentanyl concentrations were taken as estimates of the MEC for that particular patient. Samples were collected throughout the entire study period but not before every demand.

### *Clinical Monitoring*

Routine ward observations of blood pressure, pulse rate, and hourly unstimulated respiratory rates were made throughout the duration of the study.

### *Statistical Analysis*

The predictive value of anthropometric and psychological measurements for MEC and hourly fentanyl dose requirements were examined by linear regression. The MEC for each patient was taken as the mean of all the estimates for that patient. Initial studies indicated that using the logarithm of the MEC improved the fit of regression models. The maintenance dose requirement was taken as the mean hourly dose rate over the period 6–30 hours postoperatively; data from the first 6 hours were excluded because this appeared to be a period during which patients demanded large doses to achieve pseudo-steady state (see Discussion).

Prediction equations for  $\log_e$  (MEC) and maintenance dose requirements were produced in two stages.

1. Generation of a subset of models likely to include models having good predictive ability.
2. Selection of the model deemed to have the best predictive ability from the subset.

Model generation was carried out by a branching stepwise procedure. Models containing one variable were formed from each explanatory variable that significantly ( $P < 0.1$ ) correlated with the dependent variable. This comparatively high type 1 error level was chosen to reduce the risk of good models not being selected; the cost in this case is only the increased computational effort resulting from the increased size of the generated subset. Two variable models were formed from the one-variable models by adding any explanatory variable yielding a significant ( $P < 0.1$ ) improvement in fit. Thus, a single one-variable model could yield a number of two-variable models. When deletion of a variable from the model did not lead to a significantly poorer fit ( $P > 0.3$ ), the model with the variable deleted was added to the subset. No models were removed from the subset. The process was continued until all the models eligible to be in the subset had been generated.

The model in the subset having the smallest prediction error mean square was selected as the best model (PRESS technique, [27]). This method essentially chooses the model likely to have the best predictive power for patients not in the sample studied (i.e., future patients).

## **Results**

Patient characteristics, type of operation, and medication taken in the week immediately before surgery are shown in Table 1. There were 17 female and 13 male patients included in the study with an age range from 23 to 74 years and a weight range from 49 to 120 kg. There was an equal distribution of surgical procedures involving upper and lower abdominal incisions in the study patients.

The MEC values (upper panel) and the hourly fentanyl dose rate (lower panel) as a function of time in a representative patient (No. 7) who was a 33-year-old woman undergoing drainage of a hepatic cyst is shown in Figure 1. It is apparent that the fentanyl dose rate was high for the first 5 hours, between 100 and 140  $\mu\text{g/hr}$ . The hourly fentanyl dose rate then decreased to 40–60  $\mu\text{g/hr}$  for the next 30 hours, and this was further reduced to 20–40  $\mu\text{g/hr}$  for the remainder of the study. It should be remembered that the hourly fentanyl dose rate includes the basal infusion rate of 20  $\mu\text{g/hr}$  together with the 20- $\mu\text{g}$



Table 1. Anthropometric Data, Type of Operation, and Prior Medication in ODAC Study Patients

Patient No.	Sex	Age (yr)	Weight (kg)	Operation	Drugs taken in week before surgery
1	F	23	93	Cholecystectomy	—
2	F	28	73	Cholecystectomy	—
3	F	46	53	Cholecystectomy	Oxazepam, dextropropoxyphene and paracetamol, glyceryl trinitrate, colestipol, diflunisal
4	M	51	69	Selective vagotomy	Ranitidine
5	F	56	78	Cholecystectomy	Metoprolol, chlorthalidone, salbutamol aerosol, beclomethasone aerosol, chromoglycate, spironolactone
6	M	65	58	Hemicolectomy	Salbutamol aerosol, prednisolone, beclomethasone aerosol, theophylline, digoxin, verapamil
7	F	33	80	Hepatic cyst drain	Prazosin, amitriptyline
8	F	45	69	Cholecystectomy	Phenytoin, methyl phenobarbital
9	M	58	82	Sigmoid colectomy	—
10	M	54	57	Pancolectomy	Prednisolone, iron
11	F	46	77	Sigmoid colectomy	Oxazepam
12	M	32	76	Resection terminal ileum	Hydrocortisone, pethidine, oxazepam, sulphasalazine
13	M	48	89	Nissan fundoplasty	Oxazepam, amitriptyline
14	F	65	74	Cholecystectomy	Oxazepam, prochlorperazine
15	F	41	55	Gastrectomy	—
16	M	57	69	Cholecystectomy	Mylanta
17	F	31	87	Cholecystectomy	—
18	M	38	73	Division of small bowel adhesion	Oxazepam, metoclopramide
19	F	63	68	Gastrectomy	Oxazepam
20	M	64	102	Vagotomy	Ranitidine
21	F	33	49	Cholecystectomy	Spironolactone, ranitidine
22	M	63	69	Colostomy closure	—
23	F	62	71	Colon resection	—
24	M	43	120	Correction Hartman's procedure	Amitriptyline, warfarin
25	M	30	91	Appendectomy and small bowel resection	Prednisolone, sulphasalazine, azathioprine
26	F	30	77	Appendectomy	Carbimazole
27	F	55	83	Colectomy	Medroxyprogesterone, oxazepam, potassium chloride, methyldopa, methyclothiazide
28	F	74	65	Hemicolectomy	Chlorthalidone, dicyclomine, diflunisal, timolol eye drops
29	M	42	94	Closure colostomy	Bromazepam, aloxoprin
30	F	33	80	Resection liver cyst	—
Mean	17F	47	76		
SD	13M	13.9	15		
Range		23-74	49-120		

bolus "demand" doses. In contrast, however, the individual estimates of MEC (upper panel) for fentanyl were more constant throughout the study period with a mean  $\pm$  SD value of  $0.55 \pm 0.13$  ng/ml (range 0.32 to 0.76).

Summaries of hourly fentanyl dose rates and MEC data for all patients are provided in Tables 2 and 3. A mean of 22 samples (range 12 to 45) were collected per patient over a mean study duration of 50 hours (range 24 to 72). There were no cases of clinically significant decreases in respiratory rate. All patients expressed subjective satisfaction with the quality of pain relief obtained with the ODAC system.

The mean overall hourly fentanyl dose rate for the 30 patients was  $55.8 \mu\text{g/hr}$ . There was a five-fold variation from  $28.8$  to  $136 \mu\text{g/hr}$  in the mean hourly dosage requirements between individual patients (Table 2). For each particular patient, the hourly fentanyl dosage requirements varied throughout the study with generally larger doses being required in the first 6 hours after surgery than in the following 6-hour periods (Table 3). The highest dose required by any patient in any 1-hour period was  $240 \mu\text{g}$ . The mean ( $\pm$  SD) total dose administered was  $2739 \pm 1191 \mu\text{g}$  with a range of 900 to  $6260 \mu\text{g}$  (Table 3).

The mean MEC for all 30 patients was  $0.63$  ng/ml

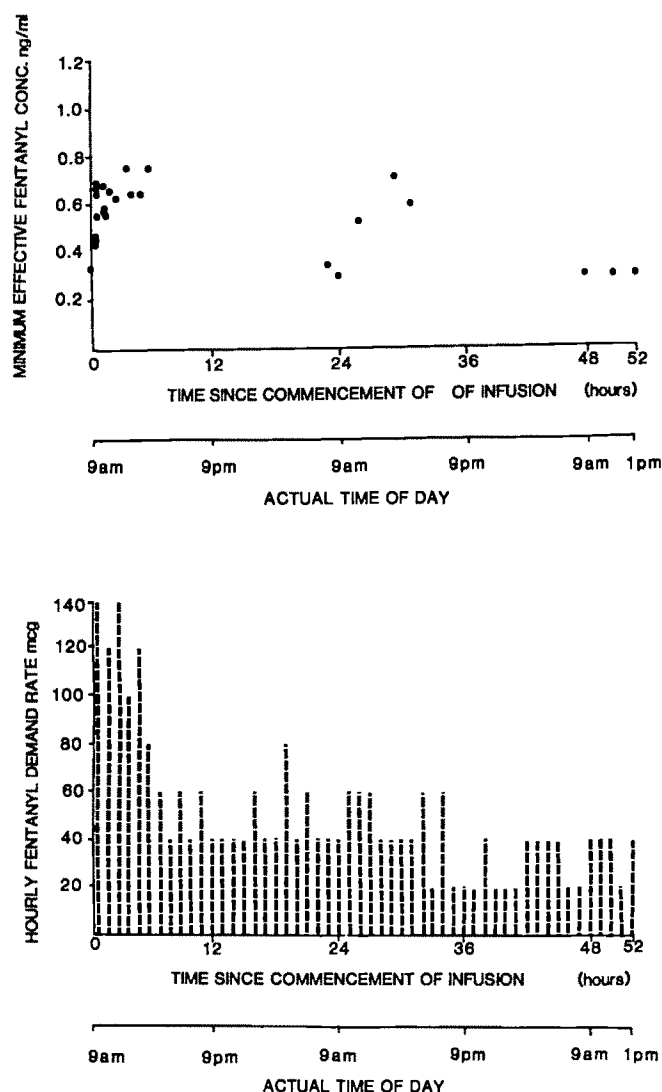


Figure 1. Graph of the minimum effective concentration (MEC) of fentanyl in blood (upper panel) and hourly fentanyl demand rate (lower panel) as a function of time in a 33-year-old woman after drainage of a hepatic cyst (patient No. 7). The postoperative pain relief was provided by ODAC. The hourly fentanyl demand rate represents a basal intravenous infusion of 20  $\mu\text{g/hr}$ , with additional 20- $\mu\text{g}$  "demand" doses available on request. The MEC represents the fentanyl concentration in blood samples collected immediately before a patient-initiated demand dose.

with a range of 0.23 to 1.18 (Table 2). The coefficient of variation in MEC within individual patients ranged from 16 to 46% with a mean  $\pm$  SD value of  $30.2 \pm 7.7\%$  (Table 2). The values for all 657 MEC determinations were log normally distributed (Fig. 2), which is consistent with previously reported data (28).

Whereas hourly fentanyl dosage rates showed a tendency to decrease with time after surgery (Fig. 3, stippled area), the MEC values for fentanyl remained relatively constant (Fig. 3). These data further demonstrate that although the dose varied markedly from hour to hour, the MEC remained relatively constant.

Table 2. Hourly Fentanyl Dose, MEC, and Coefficient of Variation in MEC for Fentanyl in the Control of Postoperative Pain Using ODAC

Patient No.	Mean overall fentanyl dose per hour ( $\mu\text{g} \pm \text{SD}$ )	Mean MEC ng/ml ( $\pm \text{SD}$ )	Coefficient of variation in MEC (%)	Number of blood samples
1	$81.8 \pm 49.2$	$1.07 \pm 0.17$	16	16
2	$33.4 \pm 17.4$	$0.33 \pm 0.12$	36	17
3	$53.3 \pm 27.6$	$0.88 \pm 0.34$	39	28
4	$84.0 \pm 34.2$	$1.03 \pm 0.29$	28	34
5	$42.9 \pm 23.5$	$0.45 \pm 0.14$	31	12
6	$81.4 \pm 52.2$	$0.64 \pm 0.21$	33	19
7	$49.6 \pm 29.0$	$0.55 \pm 0.13$	24	26
8	$37.7 \pm 22.7$	$0.23 \pm 0.10$	43	16
9	$32.7 \pm 30.0$	$0.38 \pm 0.14$	37	25
10	$46.5 \pm 34.3$	$0.49 \pm 0.13$	27	22
11	$49.7 \pm 31.1$	$0.47 \pm 0.16$	34	16
12	$136.0 \pm 51.2$	$0.94 \pm 0.24$	26	31
13	$46.5 \pm 22.9$	$0.64 \pm 0.14$	22	14
14	$33.2 \pm 27.4$	$0.31 \pm 0.12$	39	15
15	$41.5 \pm 18.5$	$0.58 \pm 0.12$	21	16
16	$28.8 \pm 16.4$	$0.44 \pm 0.10$	23	15
17	$55.0 \pm 36.0$	$0.40 \pm 0.14$	35	33
18	$51.6 \pm 35.8$	$0.39 \pm 0.18$	46	21
19	$54.8 \pm 25.6$	$0.74 \pm 0.32$	43	20
20	$41.0 \pm 23.2$	$0.52 \pm 0.14$	27	12
21	$51.2 \pm 26.8$	$1.18 \pm 0.20$	17	27
22	$49.1 \pm 28.7$	$0.63 \pm 0.14$	22	18
23	$62.6 \pm 25.0$	$0.73 \pm 0.22$	30	45
24	$65.0 \pm 32.2$	$0.76 \pm 0.20$	26	23
25	$48.1 \pm 23.1$	$0.84 \pm 0.23$	27	26
26	$38.4 \pm 24.3$	$0.43 \pm 0.16$	37	16
27	$95.8 \pm 25.0$	$0.86 \pm 0.28$	33	20
28	$48.3 \pm 21.2$	$0.57 \pm 0.18$	32	29
29	$55.9 \pm 27.9$	$0.94 \pm 0.25$	27	25
30	$78.8 \pm 39.0$	$0.54 \pm 0.12$	24	20

Mean  $\pm$  SD     $55.8 \pm 22.0$      $0.63 \pm 0.25$      $30.2 \pm 7.7$

The measured psychological and anthropometric variables had little predictive ability for MEC. The best model was

$$\log_e (\text{MEC}) = -0.73 + 0.10 \times \text{IBQ2},$$

where MEC is in nanograms per milliliter, and IBQ2 is the score on the second factor (disease conviction) of the Illness Behaviour Questionnaire (24). The adjusted  $R^2$  for this model was 0.08 showing that this model explains only 8% of the interpatient variability in  $\log_e (\text{MEC})$ .

The prediction model for the maintenance dose requirement was

$$\text{dose requirement} = 71 - 5 \times \text{IBQ1} + 9 \times \text{IBQ2} - 15 \times \text{SEX},$$

where Dose Requirement is in micrograms per hour, IBQ1 and IBQ2 are scores on the first (general hypo-

Table 3. Mean Hourly Fentanyl Doses ( $\mu\text{g}$ ) Subdivided into Six-Hourly Periods Throughout the ODAC Study

Patient No.	0-6.0	6-12.0	12-18.0	18-24.0	24-30.0	30-36.0	36-42.0	42-48.0	48+	Total cumulative dose ( $\mu\text{g}$ )
1	140	105	43	40	—	—	—	—	—	900
2	55	40	32	27	33	27	20	33	30	1635
3	90	57	30	43	47	67	57	57	48	3680
4	93	132	86	73	102	82	76	66	36	4284
5	73	93	40	53	27	27	40	30	—	1840
6	137	152	56	42	87	63	47	70	—	3665
7	117	50	43	50	50	37	27	33	—	2580
8	63	27	33	46	40	30	27	—	—	1623
9	90	43	37	43	37	11	10	10	6	1703
10	107	37	20	52	58	32	22	45	—	2232
11	60	27	33	80	75	35	37	48	—	2235
12	173	130	140	140	140	140	120	90	—	6260
13	60	40	47	72	52	27	30	50	—	2142
14	55	22	25	31	30	23	33	30	—	1347
15	50	43	43	43	57	35	32	32	25	2032
16	43	22	25	38	32	15	25	—	—	1150
17	70	126	55	78	53	53	37	47	32	3795
18	60	57	100	53	30	70	47	13	45	3717
19	67	70	60	47	43	58	42	58	35	2738
20	51	45	62	28	27	33	42	—	—	1682
21	90	47	60	57	43	30	57	67	38	3380
22	91	45	65	52	35	22	38	35	—	2210
23	73	33	57	91	63	40	73	70	—	3005
24	87	57	73	90	70	80	60	77	36	4160
25	73	53	53	53	60	47	27	29	33	2597
26	76	61	22	22	23	33	30	40	—	1846
27	113	80	87	103	83	87	97	40	—	3940
28	70	47	47	70	40	30	40	37	—	2171
29	77	40	80	83	40	37	67	63	56	3520
30	113	110	120	90	50	57	40	60	65	4100
Mean	83.9	63.0	55.8	59.7	52.7	45.8	44.8	47.3	37.3	2739
SD	30.1	36.1	28.7	26.1	25.7	27.2	23.8	19.6	14.5	1191

chondriasis) and second factors of the Illness Behaviour Questionnaire, and SEX = 1 for males and 2 for females. The adjusted  $R^2$  for this model was 0.19, indicating that this model explained 19% of the interpatient variation in dose requirements. Age, body weight, and incisional site (i.e., whether upper or lower abdominal) were not predictive for either MEC or dose requirements.

## Discussion

Postoperative pain usually comprises at least two components. First, a relatively constant pain, which may vary in intensity from time to time and, second, acute exacerbations of pain associated with specific incidents that are superimposed on the constant pain. The specific incidents may include deep breathing and coughing exercises associated with chest physiotherapy, getting in and out of bed, and minor

surgical procedures, such as removing wound drains. Therefore, postoperative pain constantly varies within certain limits. The technique of PCA allows the patient to maintain effective pain-relieving blood concentrations to reduce the pain associated with these incidents.

The MECs estimated by PCA, as in the present study, do not necessarily represent blood drug concentration above which pain is abolished. It may also be the case that different patients will experience different degrees of pain when their blood opioid concentration is held at their MEC. However, these MECs are of practical importance in that they represent blood concentrations at or below which patients will request additional analgesia. The mean coefficient of variation in MEC estimates within a particular patient was 30.2% (range 16 to 46%) based on a mean of 22 determinations per patient. This small inpatient variability in MEC, similar to that reported for methadone (18%, 5), meperidine (38%, 2) and mor-



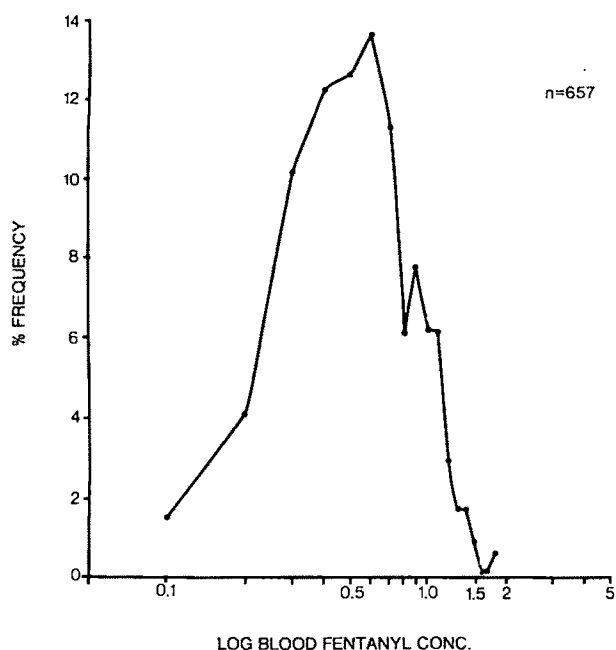


Figure 2. The percentage frequency as a function of the log fentanyl MEC. The MEC estimates were obtained in 30 patients and represent 657 values.

phine (40%, 5), suggests that patients in a PCA system used doses to maintain a minimum blood fentanyl concentration sufficient to provide analgesia. These data support the concept that a relationship exists between blood fentanyl concentration and analgesic effect within each patient. Results of animal experiments support this conclusion. For example, Ainslie et al. (29) have shown a constant ratio between fentanyl concentrations in brain and blood in dogs. Further, Hug and Murphy (30) have demonstrated that there is a close correlation between concentrations of fentanyl in plasma and cerebral spinal fluid (CSF) and the intensity of respiratory depression also in dogs. Such data show that the antinociceptive activity of fentanyl correlates with brain concentrations, which, in turn show proportionality with CSF and plasma fentanyl concentrations. In addition, duration and intensity of the respiratory depressant effects are directly proportional to fentanyl concentrations in CSF and plasma. Although in the present study the inpatient MEC values remained relatively constant over the study period, there was a five-fold variation in mean MEC values between patients (0.23 to 1.18 ng/ml). This interpatient variability in MEC is consistent with studies with other opioids (1-6).

The mean hourly dose for all patients in our study was 55.8  $\mu\text{g/hr}$ . Consistent with the MEC data, there was a large variation among patients in the mean hourly dosage input rate (range 28.8 to 136  $\mu\text{g/hr}$ ).

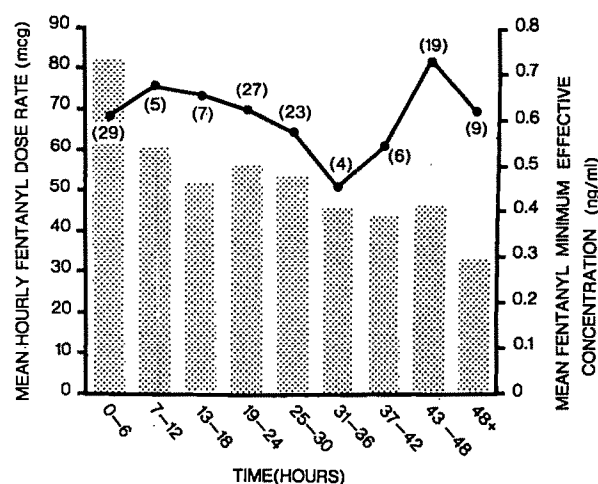


Figure 3. Graphs of mean hourly fentanyl dose (stippled area) and the corresponding mean MEC (●—●) in each 6-hour period in all 30 patients included in the ODAC study. The mean MEC estimates remained relatively constant throughout the study, whereas patients self-administered more fentanyl in the first 6 hours than in any of the ensuing 6-hour periods. Thus, patients loaded themselves initially with fentanyl and then required a lower input dose to maintain their constant MEC. The numbers in parentheses represent the number of patients who had MEC estimates performed in any 6-hour period. The 6- to 18-hour and 30- to 42-hour periods generally correspond to nighttime periods when fewer blood samples were collected.

The mean hourly dose rate (55.8  $\mu\text{g/hr}$ ) reported in this study was consistent with the data reported by Kay (31) (52.8  $\mu\text{g/hr}$  in patients having abdominal operations) but greater than the doses reported by White et al. (32) (44  $\mu\text{g/hr}$  in patients having peripheral vascular operations). In both these studies, postoperative analgesia was achieved with fentanyl delivered by ODAC systems. However, both studies were of considerably shorter duration (mean 11.0 hours [31]; mean 14.1 hours [32]) than the present study. It is possible that the lower mean hourly fentanyl dose rates in the study by White et al. may be associated with the site of the operations, i.e., peripheral vascular surgery.

In addition to the interpatient variability in mean fentanyl dose seen in the present study, the hourly fentanyl requirements for each patient also varied markedly. Patients required a larger fentanyl dosage in the first 6 hours than in the following periods. Because MEC values remained relatively constant, however, this finding suggested that patients were initially loading themselves with fentanyl to achieve an analgesic blood and brain concentration and then decreased the dose rate to maintain this concentration. This is consistent with pharmacokinetic principles that predict that for a drug administered by an intravenous infusion, four to six elimination half-lives must elapse before a steady state is attained. Therefore, mean fentanyl demand rate does not provide an

accurate representation of the blood concentration data, which is proportionally related (29,30) to the concentration of fentanyl in the brain, the determinant of the pharmacodynamic effects.

A similar pattern of dosing has been observed in studies of other opioids. Chakravarty et al. (33) reported dose requirements for meperidine and buprenorphine administered via PCA machines postoperatively to be the greatest during the first 3 hours after surgery for patients who had undergone surgery involving an abdominal incision. In the next 3-hour period, the dose administered decreased to approximately 60% of the initial 3-hour period, then steadily decreased up to 24 hours after operation.

Psychological factors were found to have some predictive value for MEC and maintenance dose requirements. The dose requirement was also influenced by patient gender. Our model predicts lower dose requirements for females, whereas patients with high scores on IBQ2 (disease conviction) are predicted to have higher MECs and higher dose requirements. These factors, however, contribute only a small amount to the variation among patients in MEC and dose requirements as the models account for only 8% and 19% of the variation in  $\log_e$  (MEC) and dose requirements, respectively. This finding suggests that many other factors not examined in this study are also important determinants of MEC and dose requirement.

Why is there such a marked interpatient variation in MEC beyond that explicable by our regression model? Reasons for the marked variability in MEC can be subdivided into pharmacokinetic, pharmacodynamic, and psychological factors.

Pharmacokinetic differences between patients in the binding of fentanyl to plasma proteins may provide part of the explanation. Only unbound drug is available for passage across the blood-brain barrier. Approximately 80% of fentanyl is bound to plasma proteins (34). Fentanyl is a basic drug and is bound to acute phase proteins such as  $\alpha$ -1 acid glycoprotein (AAG) (35). It has been reported that the concentrations of AAG may increase in certain disease states (36), which could therefore lead to increased binding and a decrease in the amount of free drug available for passage across the blood-brain barrier.

Variation between individuals in blood and CSF concentrations of endogenous opioids (e.g., endorphins) may be a further factor contributing to variations in MEC and dose requirements for fentanyl. Patients with higher CSF or plasma concentrations of endogenous opioids may require less exogenous opioid to achieve satisfactory control of postoperative pain (37-39).

Although it is universally acknowledged that psychological factors are important in the treatment of postoperative pain, the prediction of analgesic requirements for an individual from psychological test scores is difficult. Of all the personality traits examined in this study, only those measured by the Illness Behaviour Questionnaire had predictive value for dose requirements or mean MEC. This contrasts with the results of other studies (17-21) that suggest that increased postoperative opioid administration is required for patients who score highly on extroversion and neuroticism scales.

No cases of clinically significant depression of respiratory rate were observed during the study, which is consistent with the results of other studies performed with fentanyl delivered by ODAC infusion pumps (31,32). The lack of respiratory depression was not surprising because the MEC values generated in this study ranged from 0.23 to 1.18 ng/ml, below the reported concentration of approximately 2 ng/ml required to produce clinically significant respiratory depression (11).

In summary, this study suggests a relationship between blood fentanyl concentration and analgesic effect as indicated by a small coefficient of variation (mean value of 30%) for multiple estimates of MEC in patients undergoing surgical procedures involving an abdominal incision. The mean MEC obtained in this study was 0.63 ng/ml. The five-fold (0.23 to 1.18 ng/ml) interpatient variation in the MEC is consistent with the results obtained in studies with other opioids. The reasons for this variability are complex and could be attributed to several different psychological, pharmacodynamic, or pharmacokinetic factors. The MEC data reported in this communication will help to provide a basis for establishing the blood fentanyl concentrations necessary for effective postoperative pain relief following alternative routes of administration such as transdermal fentanyl.

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## Spinal Anesthesia and Lumbar Lordosis

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LOGAN MR, DRUMMOND GB. Spinal anesthesia and lumbar lordosis. *Anesth Analg* 1988;67:338-41.

*Hyperbaric bupivacaine 0.5% (3.0 ml) was injected intrathecally in two groups of 20 patients. Both groups of patients lay in the lateral position with their hips flexed at 90°. In group F, the hip flexion was maintained for 5 minutes after turning supine. In group S, the hips were straightened before the patients were turned to the supine*

*position. The technique of hip flexion to reduce the lumbar lordosis did not significantly limit the height of anesthetic blockade. The distribution of height of anesthetic blockade showed marked bimodality ( $P < 0.05$ ) in both groups, in group F at T4 and T9 and in group S at T3 and T9. Cardiovascular side effects were minimal and equal in both groups.*

Key Words: ANESTHETIC TECHNIQUES—spinal.

Since Barker's demonstration of the motion of hyperbaric solutions within "glass spines" in 1907 (1), positioning and tilting of the patient during and after intrathecal injections of local anesthetic solutions of various baricities have become common practices to influence the spread of the resultant blockade (2,3). In supine patients, a downward slope between the lumbar lordosis and the thoracic kyphosis would encourage "pooling" of a hyperbaric solution in the thoracic hollow. Lumbar lordosis can be reduced by flexion of the hips (4). Using hyperbaric tetracaine, Smith (4) reduced the cephalad extent of anesthetic blockade by 1.5 to 2 dermatomes by maintaining flexion of the patient's hips for 2 to 3 minutes once they had been turned into the supine position. This maneuver flattened the lumbar lordosis and produced a unimodal distribution of the upper extent of the block with a modal value of T8. In those whose hips were straight, there was a marked bimodal distribution with modal values at T4 and T8. However, in Smith's study the assessor of the block was not blind to the patient position. The present study was undertaken using a blind assessment method to determine the effect of reducing lumbar lordosis by hip flexion on the extent of analgesic and anesthetic blockade, and on cardiovascular side effects, after spinal anesthesia with hyperbaric bupivacaine.

### Patients and Methods

Forty patients (ASA 1 or 2) of either sex, 20-70 years old, who were to undergo elective surgery to the lower limb or perineum under spinal anesthesia, gave informed consent to take part in the study. Approval was obtained from the hospital ethics committee. Each patient was premedicated with temazepam 20 mg orally approximately 1 hour before anesthesia. A peripheral venous cannula was inserted and an infusion of lactated Ringer's solution started. The volume administered was limited to <100 ml until the end of the assessment period. Patients were randomly allocated to one of two groups either to maintain hip flexion (group F) or allowed to lie supine with straight legs (group S) after the subarachnoid injection had been given. Lumbar puncture was performed with all the patients in the left lateral position using a 25-g spinal needle at the L2-3 interspace with a standard midline approach. The patient's spinal column, including the neck, was kept as horizontal as possible during the lumbar puncture. Three ml 0.5% bupivacaine in 8% glucose was injected over exactly 20 seconds. Immediately after this the patient was moved gently into the supine position. In group F, the flexion of the lumbar spine necessary to perform the lumbar puncture was maintained throughout this movement and for the 5 minutes after the injection, by keeping the hips flexed at 90°. Five minutes after the injection, the legs were gently straightened and laid flat on the operating table. In group S, the patients' hips and knees were straightened before turning supine.

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Table 1. Patient Data\*

	Group F (flexed hips)	Group S (straight hips)
Age (yr)	45.6 ± 12.1	46.1 ± 10.4
Height (cm)	166 ± 7.9	167 ± 9.7
Weight (Kg)	68.6 ± 14.6	70.4 ± 11.8

\*Data are ± sd.

Nerve blockade was assessed by an observer unaware of whether or not hip flexion had been maintained. The cephalad spread of analgesia, anesthesia, and the degree of motor weakness in the legs were assessed at 5-minute intervals for 30 minutes. Analgesia was defined as inability to appreciate pinprick, and anesthesia as the inability to appreciate touch. Motor blockade was determined according to a modified Bromage scale (5) as follows: 0 = ability to raise extended leg against gravity, 1 = inability to raise extended leg, 2 = inability to flex the knee, 3 = inability to flex the ankle. Arterial pressure (by sphygmomanometry) and heart rate were recorded before the patient was positioned for lumbar puncture and at 5-minute intervals for 30 minutes after injection.

Statistical analyses were made using Wilcoxon signed rank, Wilcoxon rank sum, Fisher's exact (6) and Silverman (7) tests as appropriate.

## Results

Details of the patients are given in Table 1. There were no significant differences between the groups in regard to age, sex, height, or weight.

The upper extents of anesthesia and analgesia are shown in Figure 1. Although in both groups the mean levels of analgesia and modal values of anesthesia were one segment higher on the left side of the body, this difference was not statistically significant. The values used for further analysis were the most cephalad regardless of the side of the body. The distribution of the upper extent of anesthesia in both groups 30 minutes after the injection showed bimodality ( $P = 0.03$ , Silverman test). This was more pronounced in group S than in group F. The bimodality was apparent 5 minutes after the injection and became more obvious when the height of block was assessed at later times. The two modal values were similar in the two groups, with group F at T4 and T9 and group S at T3 and T9. However the range of values in group F (T2-L5) was larger than in group S (T1-L1).

In contrast to anesthesia, the upper extent of analgesia showed no statistically significant bimodal-

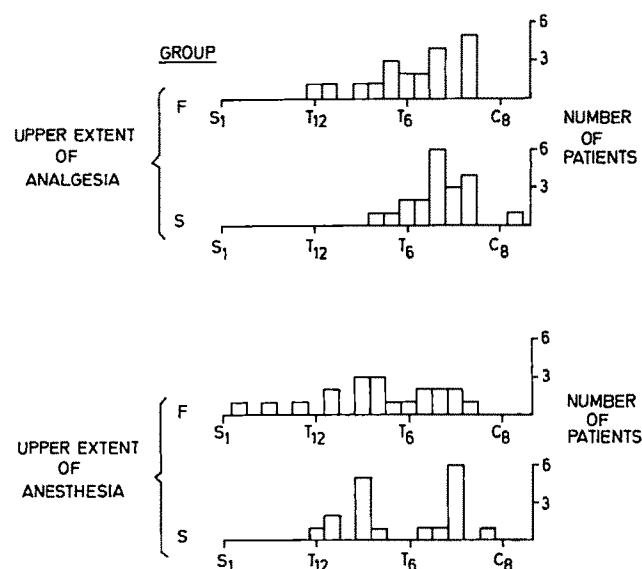


Figure 1. Distribution of the upper extent of analgesic and anesthetic blockade in the two groups.

ity in either group. There was, however, a bimodal tendency at 5 minutes in those with their legs straight. This tendency was not seen in later assessments. At 30 minutes, both groups showed unimodal distributions of analgesia with group F skewed caudally. The mean cephalad spread of analgesia was to  $T5 \pm 3.0$  sd in group F and to  $T4 \pm 1.9$  sd in group S. The levels of analgesia and anesthesia were not related to the patient's sex, height, weight, or degree of obesity (weight/expected weight%).

Four patients in the "flexed-hip" group did not attain full motor blockade of the lower limbs. Three could dorsiflex their ankles. One patient had no motor block with an accompanying low analgesic block to T11 and anesthetic block to L5. Only one patient in the "hips-straight" group did not attain full motor blockade and could dorsiflex his ankles.

There were no significant differences in the mean heart rates and arterial blood pressures between the two groups. One patient in each group had a decrease in systolic pressure of more than 30% from the preanesthetic value. Paresthesia of the hands occurred in four patients, all of whom were in the hips-straight group. Three patients, who were all in group F, had inadequate blocks for surgery to the lower limbs and were given general anesthesia. Two patients in group F developed typical postspinal headaches with photophobia and postural headache.

## Discussion

Smith (4) demonstrated that flexing the hips and decreasing the lumbar lordosis reduced the height of

the block after an intrathecal injection of hyperbaric amethocaine. He noted bimodality in the distribution of the height of anesthesia in patients turned supine and allowed to lie with their hips straight. On the other hand, flexion of the hips produced a unimodal distribution of height of blockade. However, a major disadvantage of the study by Smith was that assessment of block height was not performed by a separate assessor. The present study was designed to reevaluate this finding and showed that there was similar bimodality of the cephalad extent of anesthetic blockade, using hyperbaric bupivacaine and with the extent of block assessed by an independent observer. This bimodality was greater when the hips were kept straight but was also seen when they were kept flexed. We believe that the mechanism proposed by Smith (4) to explain his observations can be used to explain our data.

When a patient is turned into the supine position after a midlumbar subarachnoid injection of a hyperbaric solution, the injected dose will be split into a part that migrates in a cephalad direction and a part that flows caudally. A point of maximum lumbar lordosis situated in the upper lumbar region will reduce the amount of agent that moves in a cephalad direction. Because a greater amount of drug is necessary to cause anesthesia than analgesia, any difference between the two maneuvers is likely to be more obvious when anesthesia is studied. In contrast, even small quantities of the agent migrating cranially may be sufficient to provide analgesia. Consequently, although we found clear evidence of the bimodal extent of block when anesthesia was assessed, the distribution of the upper extent of the analgesic block was unimodal, with a skew in the caudal direction.

The more marked bimodality seen in patients whose hips were straight may be due in part to a more lordotic lumbar spine affecting the "splitting ratio" of the hyperbaric solution. Levin et al. (8) compared intrathecal isobaric and hyperbaric tetracaine in patients being placed early into the lithotomy position. However, they only studied the analgesic component of the blockade and found no significant difference in the extent of blockade with these two baricities. In addition, their patients were sitting during the intrathecal injection, a position which limits the cephalad spread of hyperbaric amethocaine (8). The sitting position directs the hyperbaric solution caudally, altering the "splitting ratio" once the patient is turned supine. Lithotomy position will tend to flatten the lumbar lordosis, which would help to reduce the caudal migration of the hyperbaric solution, offsetting some of the gravitational movement

Table 2. Sensory and Motor Blockade and Cardiovascular Values in Patients with and without Hip Flexion after Intrathecal Hyperbaric Bupivacaine 0.5%\*

	Group F	Group S
No. of patients	20	20
Position of hips	flexed	straight
Level of analgesia	T5 $\pm$ 3.0	T4 $\pm$ 1.9
Mode level of anesthesia	T4 and T9	T3 and T9
Range of anesthesia	T2-L5	T1-T12
Motor blockade (% with complete block)	80	95
Heart rate (beat/min)		
Before	84 $\pm$ 12	81 $\pm$ 14
After 30 minutes	74 $\pm$ 13	71 $\pm$ 17
Systolic pressure (mm Hg)		
Before	121 $\pm$ 13	127 $\pm$ 17
After 30 minutes	100 $\pm$ 13	103 $\pm$ 15

\*Data are  $\pm$  SD.

occurring while the patient was in the sitting position.

In the supine patient, the sacral segment of the subarachnoid space lies almost vertically, creating a sump for the caudally migrating portion of the dose. This means that the resultant effect of the "splitting" of the dose might be determined early in the migration of the injected dose. This could account for the occasional patient with a low lumbar anesthetic block only, such as occurred in three of our patients in the flexed group (Table 2). Positioning the patient with a noticeable head-down tilt during the injection, as described by Nicholson (2) and Lee and Atkinson (3), would minimize this sump effect and permit cephalad movement of the solution before turning the patient supine. This would result in the "splitting" favoring cephalad spread of the solution.

The significant bimodal distribution of anesthetic block seen in this study highlights the importance of the appropriate selection of statistical tests when hyperbaric intrathecal injections are studied. Also, assuming a continuous distribution of data relating to local anesthetic blockade when performing statistical analysis is, strictly speaking, incorrect because the extent of the block is expressed with an interval scale (e.g., L2, L3, L4). However, for many purposes, interval data are handled using tests that should strictly be restricted to continuous data (e.g., 2.1, 4.3, . . . 5.1), such as Student's *t*-test. It may be that in previous studies of hyperbaric agents, bimodal distribution of block height was present, and inappropriate use of statistical tests that assume normally distributed, continuous data may have resulted in incorrect conclusions.

We conclude that the technique of hip flexion during induction of spinal anesthesia to reduce the



lumbar lordosis does not significantly limit the height of anesthetic blockade, nor does it influence the cardiovascular effects of spinal blockade. Hip flexion results in a wider range of height of anesthetic block, which reflects a poorer predictability of block. Importantly, the bimodal distribution of anesthetic blocks found when the block develops with the patient in the horizontal supine position is highlighted by the change to a more normal distribution when lumbar lordosis is reduced by hip flexion.

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## Midazolam–Thiopental Anesthetic Interaction in Patients

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TVERSKOY M, FLEYSHMAN G, BRADLEY EL Jr, KISSIN I. Midazolam–thiopental anesthetic interaction in patients. *Anesth Analg* 1988;67:342-5.

*The effect of thiopental on the induction dose–response curve for midazolam was studied in nonpremedicated ASA physical status I and II patients. As an endpoint of anesthesia, ability to open eyes on command was used. Dose–response curves for thiopental, midazolam, and their combination were determined with a probit procedure and*

*compared with an isobolographic analysis. Interaction between midazolam and thiopental was found to be synergistic (supraadditive). The degree of midazolam–thiopental anesthetic synergism in surgical patients was close to that reported previously in rats with loss of the righting reflex as an index of anesthesia.*

Key Words: ANESTHETIC, INTRAVENOUS—midazolam, thiopental. INTERACTIONS, DRUGS—barbiturates, benzodiazepines.

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The combined effect of midazolam and thiopental on the righting reflex in rats is synergistic (1), perhaps related to the ability of barbiturates to modulate benzodiazepine receptors. Barbiturates, which allosterically enhance the binding of benzodiazepines to the benzodiazepine receptors (2–5), along with their own anesthetic action, also should enhance the anesthetic effect of benzodiazepines. As a result, the combined effect of a barbiturate and a benzodiazepine should be more than the sum of the effects of the two agents acting separately. The present study was designed to test the hypothesis that midazolam–thiopental anesthetic interaction is synergistic in patients as has been demonstrated to occur in rats.

### Methods

Ninety unpremedicated ASA physical status I or II adult (21 to 51-year-old) female patients scheduled for diagnostic curettage or other minor gynecologic procedures participated in the study, which was approved by the Institutional Review Board. Three groups were studied: one group received thiopental,

and two others received either midazolam or midazolam–thiopental combination. Each group comprised 30 patients. The data obtained in the thiopental group were used to determine the dose of thiopental administered in the midazolam–thiopental group: 0.7 mg/kg (one-quarter of ED<sub>50</sub>). Next, midazolam dose–response curves with and without the addition of thiopental 0.7 mg/kg were determined. As an endpoint of anesthesia the abolition of the ability to open eyes on command was used. If the patient did not respond to the command, she was assumed to be unconscious.

The study was carried out in a double-blind manner, the response to the command being checked by an investigator unaware of what drug or dose was used. The following predetermined doses of drugs each in a subgroup of five patients were administered: in the thiopental group (mg/kg): 1.7, 2.0, 2.3, 2.6, 3.0, 3.6; in the midazolam group (mg/kg): 0.07, 0.10, 0.13, 0.19, 0.26, 0.37; in the midazolam–thiopental group (mg/kg): 0.03 and 0.7, 0.04 and 0.7, 0.06 and 0.7, 0.08 and 0.7, 0.11 and 0.7, 0.15 and 0.7 (midazolam and thiopental, respectively). Patients were assigned to the subgroups randomly.

All drugs were injected intravenously in a constant volume of 10 ml over 15 seconds. In the midazolam–thiopental group, midazolam was injected first; followed 1 minute later by thiopental; the endpoint—unconsciousness—was determined 3 minutes after the first injection. In the midazolam group, midazolam was injected first, 1 minute later 10 ml of saline

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Table 1. Characteristics of Patients (Mean  $\pm$  SD)

Variable	Groups		
	Thiopental	Midazolam	Thiopental-midazolam
Age (years)	33 $\pm$ 5	34 $\pm$ 6	35 $\pm$ 5
Weight (kg)	63 $\pm$ 4	62 $\pm$ 9	65 $\pm$ 5
Number of patients (all female)	30	30	30

was injected and 3 minutes after the first injection the endpoint of anesthesia was checked. In the thiopental group, the endpoint was determined 2 minutes after its injection. After determination of the response to verbal command to open the eyes, all patients received another dose of an intravenous anesthetic to obtain an adequate depth of anesthesia before starting the surgical procedure.

The percentages of patients unable to open their eyes were converted into probit values and plotted against logarithmic value for the respective dose. Dose-response curves were determined with the use of probit analysis (6). To define the type of interaction between midazolam and thiopental, isobolographic analysis was used ( $ED_{50}$  level) (7).  $ED_{50}$  values from all groups of patients were plotted in a form of an isobologram (see an illustration in Fig. 3). Single-drug  $ED_{50}$  points were placed on the dose coordinates of the isobologram and a combined  $ED_{50}$  point in the dose field. The deviation of a combined  $ED_{50}$  point from an additive line (straight line joining single-drug  $ED_{50}$  points) was measured as the length along a line running from the point in question to the additive line perpendicular to it. The standard error of this distance was computed by the method of propagation of error (8), and error estimates from a combined  $ED_{50}$  point, as well as single-drug  $ED_{50}$  points, were used. An approximate *t*-test used to test the assumption of additivity was then obtained as the ratio of the measured distance to its standard error (9).

## Results

The study groups were comparable with respect to age and weight (Table 1). The thiopental dose-response curve for induction of anesthesia is presented in Figure 1. The thiopental  $ED_{50}$  value obtained from this curve was 2.9 mg/kg (95% confidence limits, 2.5–3.8 mg/kg). Figure 2 represents the midazolam dose-response curves for induction of anesthesia with and without the addition of 0.7 mg/kg thiopental (approximately one-quarter of the thio-

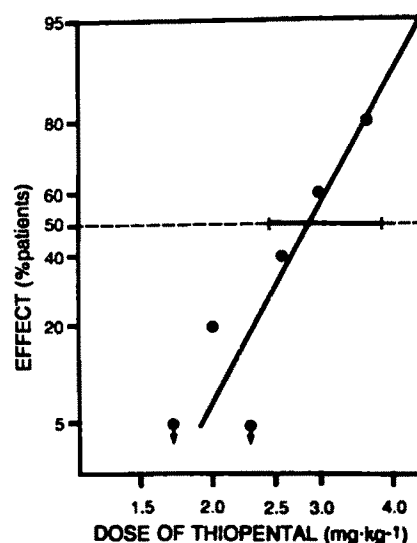


Figure 1. Thiopental quantal dose-response curve for induction of anesthesia. Along the vertical axis, the percentage of patients (on a probit scale) who did not open their eyes in response to the command. Along the horizontal axis, doses of thiopental (on a log scale). Each dot represents a subgroup of five patients at the indicated dosage. A horizontal line at the  $ED_{50}$  level indicates 95% confidence limits.

pental  $ED_{50}$  value). The addition of thiopental markedly shifted the midazolam dose-response curve to the left along the dose axis. The midazolam  $ED_{50}$  value was 0.19 (0.12–0.34) mg/kg, and it decreased to 0.05 (0.04–0.07) mg/kg with the addition of thiopental. There was also a tendency for the change in the slope of the midazolam dose-response curves. However, the difference between the slopes of the two curves did not reach the level of statistical significance.

The midazolam-thiopental isobologram is presented in Figure 3. The combined  $ED_{50}$  point for induction of anesthesia deviates to the left of the additive line (joining the single-drug  $ED_{50}$  points) indicating synergism (supraadditive interaction). Comparison of the combined and single-drug  $ED_{50}$  doses is presented in Table 2. In combination, the sum of the fractional doses was significantly lower than a single-drug fractional dose (0.5 vs 1.0,  $P < 0.001$ ). The ratio of a single-drug fractional dose to a combined dose was 2.0. Thus, the table shows that approximately one-fourth of the single-drug dose for each of the two agents was needed in combination to induce anesthesia in 50% of the patients.

## Discussion

The thiopental  $ED_{50}$  value of 2.9 mg/kg obtained in this study is close to the  $ED_{50}$  value for thiopental



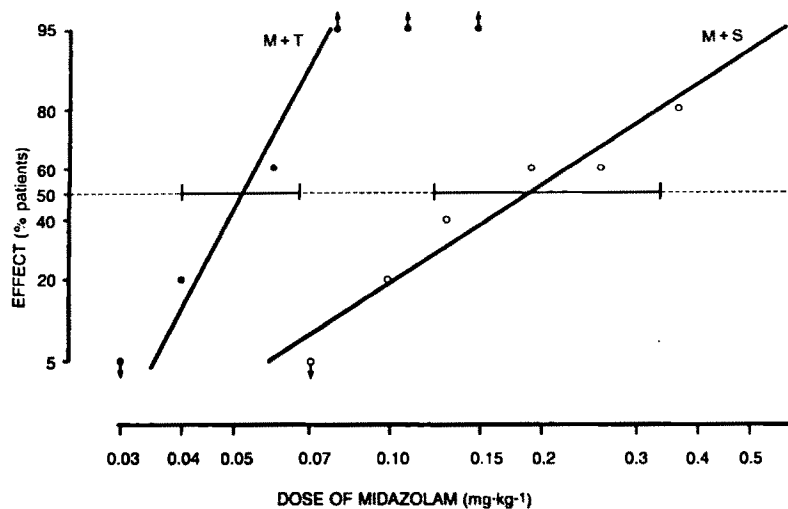


Figure 2. Midazolam quantal dose-response curves for induction of anesthesia with and without the addition of thiopental. M + T, dose-response curve for midazolam (M) with the addition of 0.7 mg/kg thiopental (T) (a constant dose that equals one-quarter of the thiopental ED<sub>50</sub> value, see Methods). M + S, dose-response curve for midazolam with the addition of saline (S) instead of thiopental. Each dot represents a subgroup of five patients at the indicated dosage (closed for M + T, open for M + S).

Table 2. Midazolam-Thiopental Anesthetic Interaction

Groups <sup>a</sup>	Equi-effective doses (ED <sub>50</sub> ) of midazolam–thiopental combination					Ratio <sup>b</sup>
	Midazolam component		Thiopental component		Sum of fractional doses	
	Fraction of ED <sub>50</sub>	Dose (mg/kg)	Fraction of ED <sub>50</sub>	Dose (mg/kg)		
M <sup>b</sup>	1.00	0.19 (0.12, 0.34) <sup>c</sup>	0.00	0.00	1.0	2.0
M+T	0.26	0.05 (0.04, 0.07)	0.24	0.7 <sup>d</sup>	0.5 <i>P</i> < 0.001	
T	0.00	0.00	1.00	2.9 (2.5, 3.8)	1.0	

<sup>a</sup>M, midazolam group; M+T, combined midazolam-thiopental group; T, thiopental group.

<sup>b</sup>Ratio of single-drug fractional dose to combined fractional dose.

<sup>c</sup>Confidence limits in parentheses.

<sup>d</sup>Dose was kept constant (see Methods).

reported by Stella et al. (10) (in premedicated patients)—2.2 mg/kg. Our midazolam ED<sub>50</sub> value was 0.19 mg/kg. Midazolam ED<sub>50</sub> values reported in the literature for the same endpoint are 0.13 mg/kg (11) and 0.19 mg/kg (cumulative doses) (12). Wide differences in the induction doses of midazolam reported by different authors are well known and has been reviewed recently (13).

The isobolographic analysis used in the present study demonstrated synergistic midazolam-thiopental interaction for induction of anesthesia (abolition of the response to verbal command). In other words, one-quarter of the thiopental ED<sub>50</sub> reduced the midazolam anesthetic requirement (for ED<sub>50</sub> level) by three-quarters. The degree of midazolam-thiopental synergism obtained in surgical patients is very close to that reported in rats with the use of loss of the righting reflex as an index of anesthesia (1). The ratio of single-drug fractional dose to combined midazolam-thiopental fractional dose was 2.0 in patients and 2.6 in rats. The similar type and

even degree of midazolam-thiopental anesthetic interaction in humans and in rats makes the rat an adequate model for analysis of the mechanism of the observed synergism. The first step in such analysis would be an exclusion of pharmacokinetic factors contributing to the midazolam-thiopental synergism.

As far as pharmacodynamic mechanisms are concerned, the following possibility can be considered: The benzodiazepine receptor, the GABA (gamma-aminobutyric acid) receptor, and the barbiturate-binding sites are part of a supramolecular complex, and binding of a drug to one of the sites of this complex can allosterically modify the benzodiazepine receptor (14). It has also been shown that barbiturates enhance binding of benzodiazepines to the benzodiazepine receptor (2-5). The synergistic anesthetic interaction between midazolam and thiopental may be explained on this basis. In conclusion, midazolam-thiopental interaction in patients results in a synergism regarding induction of anesthesia.

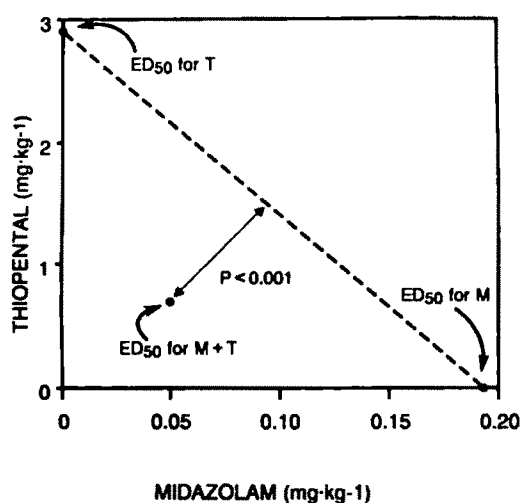


Figure 3.  $ED_{50}$  isobologram for the anesthetic interaction of midazolam and thiopental.  $ED_{50}$  values generated by probit analysis indicate the dose level that provides the effect in 50% of the patients. T and M are  $ED_{50}$  values for midazolam and thiopental given alone. M + T is  $ED_{50}$  value for the midazolam–thiopental combination. The dashed straight line connecting the single-drug  $ED_{50}$  points, T and M, is an additive line.  $P$  value indicates the level of statistical significance for deviation of the combined  $ED_{50}$  point to the left of the additive line, indicating a synergism.

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## Thiopental Does Not Alter $\text{Ca}^{2+}$ Uptake by Cardiac Sarcoplasmic Reticulum

Thomas J.J. Blanck, MD, PhD, and Robert L. Stevenson, MD

BLANCK TJJ, STEVENSON RL. Thiopental does not alter  $\text{Ca}^{2+}$  uptake by cardiac sarcoplasmic reticulum. *Anesth Analg* 1988;67:346-8.

*The effect of thiopental on  $\text{Ca}^{2+}$  uptake by cardiac sarcoplasmic reticulum (SR) isolated from the rabbit was examined to clarify the role of the sarcoplasmic reticulum in the negative inotropic action of thiopental. Thiopental, from 0 to 378  $\mu\text{M}$ , did not alter the rate of  $\text{Ca}^{2+}$  uptake by the SR. We also compared the ATP dependence of  $\text{Ca}^{2+}$  uptake in*

*the presence and absence of 284  $\mu\text{M}$  thiopental. The  $K_m$  for ATP and the  $V_{max}$  of  $\text{Ca}^{2+}$  uptake were unaffected by thiopental. It is concluded that thiopental does not alter  $\text{Ca}^{2+}$  uptake by the SR and that the negative inotropic effects of thiopental occur at other sites in the myocardial cell.*

Key Words: ANESTHETICS, INTRAVENOUS—thiopental. HEART, MYOCARDIAL FUNCTION— $\text{Ca}^{2+}$  uptake. IONS—calcium.

Thiopental, a commonly used intravenous anesthetic, is a known depressant of cardiac contractility (1). The mechanism by which thiopental depresses cardiac contractility is still uncertain, but previous reports have suggested thiopental induces changes in sarcolemmal and sarcoplasmic reticulum (SR) function. The sarcoplasmic reticulum is a  $\text{Ca}^{2+}$ -sequestering organelle important in the control of contraction and relaxation. Alteration in the binding of  $\text{Ca}^{2+}$  to cardiac sarcoplasmic reticulum by barbiturates has been observed (1-3). Nayler and Szeto (2), for example, found an increased relaxation time in canine trabecular muscle exposed to pentobarbital but did not observe a dose-dependent alteration in microsomal  $\text{Ca}^{2+}$  uptake from 0 to 2.0 mM pentobarbital. On the other hand, Lain et al. (3) did find a dose-dependent decrease in SR  $\text{Ca}^{2+}$  uptake by pentobarbital at 1-3 mM. We have examined the effect of the thiobarbiturate, thiopental, on rabbit ventricular SR  $\text{Ca}^{2+}$  uptake to clarify the possible role of one negative inotropic site of action.

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### Methods

Rabbit cardiac sarcoplasmic reticulum was prepared by the method of Harigaya and Schwartz (4). Calcium uptake experiments were performed in  $12 \times 75$ -mm glass test tubes. The reaction medium consisted of 100 mM KCl, 5 mM  $\text{MgCl}_2$ , 5 mM sodium azide, 0.1 mM  $\text{CaCl}_2$ , 50 mM 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid (Hepes) with  $^{45}\text{CaCl}_2$  (140,000 cpm/sample). Experiments were performed at  $37^\circ\text{C}$ , pH 7.4, and the reaction was initiated by the rapid sequential addition of 5 mM ATP and 100  $\mu\text{g}$  of SR. An aqueous solution of thiopental was added to the reaction medium before the addition of ATP and SR. The rate of calcium uptake was estimated by a 2-minute incubation. Aliquots of the reaction medium were sampled at 2 minutes and placed on Whatman GFF glass-fiber filters under vacuum. Each filter was rinsed with 20 ml ice-cold  $\text{CaCl}_2$ , air dried, and placed in 5 ml of scintillation fluid.  $^{45}\text{Ca}$  accumulated in the SR was quantified by liquid scintillation counting of the SR vesicles retained on the GFF filters.  $^{45}\text{Ca}$  counting efficiency was approximately 95%.

Protein was measured by the method of Bradford (5). Water used for reagents was distilled and deionized. All chemicals were reagent grade. Hepes was purchased from Calbiochem-Behring Corporation.  $^{45}\text{CaCl}_2$ , 10 mCi/ml, was purchased from New England Nuclear Company. GFF filters were purchased from Whatman, Inc.



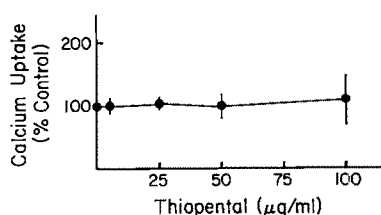


Figure 1. The dependence of canine cardiac sarcoplasmic reticulum  $\text{Ca}^{2+}$  uptake on thiopental concentration. Experimental conditions as described under Methods. The data are expressed as percentage of control. The data are the means of observation from four independent experiments  $\pm$  sd. The following are the equivalent molar concentrations of thiopental: 25  $\mu\text{g/ml}$ , 94.6  $\mu\text{M}$ ; 50  $\mu\text{g/ml}$ , 189  $\mu\text{M}$ ; 100  $\mu\text{g/ml}$ , and 378  $\mu\text{M}$ .

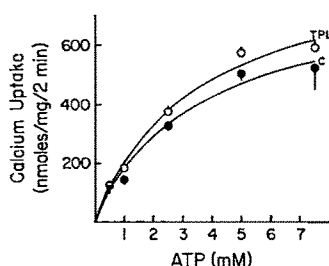


Figure 2. The ATP dependence of  $\text{Ca}^{2+}$  uptake in the presence and absence of 75  $\mu\text{g/ml}$  (284  $\mu\text{M}$ ) thiopental. Experimental conditions as described under Methods. Each point is the mean of three observations  $\pm$  sd. The curves were generated from the Michaelis-Menten equation using the values of  $K_m$  and  $V_{\max}$  obtained from weighted nonlinear regression analysis.

## Results

To observe whether thiopental exposure had any effect on  $\text{Ca}^{2+}$  uptake by cardiac SR, the SR membranes were added to a solution containing thiopental to initiate the  $\text{Ca}^{2+}$  uptake reaction. Figure 1 demonstrates the effect of increasing concentrations of thiopental on  $\text{Ca}^{2+}$  uptake at 5 mM ATP. The data are presented as the percentage uptake activity relative to activity in the absence of thiopental (TPL):

$$\frac{(\text{Ca}^{2+} \text{ uptake}_{\text{TPL}})}{(\text{Ca}^{2+} \text{ uptake}_{\text{TPL}=0})} \times 100\% = \% \text{ Ca}^{2+} \text{ uptake.}$$

Each data point is the mean of duplicate samples of four experiments. The data demonstrate that thiopental over the concentration range studied had no effect on SR  $\text{Ca}^{2+}$  uptake.

The ATP dependence of  $\text{Ca}^{2+}$  uptake is shown in Figure 2. Thiopental slightly stimulated uptake over the entire ATP range. Statistical estimates of  $K_m$  and  $V_{\max}$  were determined by weighted nonlinear regression analysis (Table 1) (6). There was no statistically significant difference between control and thiopental-treated SR for either of these parameters. The curves in Figure 2 were generated from insertion of the  $K_m$  and  $V_{\max}$  values into the Michaelis-Menten equation.

Table 1. The Effect of Thiopental (75  $\mu\text{g/ml}$ ) on the Michaelis-Menten Constants

	$K_m$ (mM $\pm$ se)	$V_{\max}$ (nmol/mg/2 min $\pm$ se)
Control	3.47 $\pm$ 0.86	799 $\pm$ 95.7
Thiopental	3.41 $\pm$ 0.84	899 $\pm$ 98.1

## Discussion

Previous investigations have examined the effect of pentobarbital, the oxybarbiturate counterpart of the thiobarbiturate, thiopental, on cardiac SR  $\text{Ca}^{2+}$  uptake. At concentrations significantly higher than those at which the negative inotropic effects of pentobarbital have been observed, Lain et al. (3) found a depression of  $\text{Ca}^{2+}$  uptake. They noted a 10% decrease in  $\text{Ca}^{2+}$  uptake ability at 0.6 mM pentobarbital, a concentration at which other investigators have reported a 30–40% decrease in contractile activity. No statistical analysis was performed by Lain et al. (3) on their data, but the standard error of the measurement overlapped the value for the nonpentobarbital-treated SR. In our studies we have examined the effect of thiopental on  $\text{Ca}^{2+}$  uptake over the thiopental concentration range in which Frankle and Poole-Wilson had noted a dose-dependent depression of contractile function in a rabbit septal preparation (1). At 5 mM ATP, the approximate intracellular ATP concentration, there is essentially no effect of thiopental on  $\text{Ca}^{2+}$  uptake over a broad thiopental range. Similarly, over a broad range of ATP concentrations, thiopental has no apparent physiologically significant effect on  $\text{Ca}^{2+}$  uptake.

Komai and Rusy (7) examined the effect of thiopental on the physiologic response of isolated rabbit papillary muscles. They found that thiopental: 1) decreased steady state contractions in a dose-dependent manner; 2) decreased the positive staircase; 3) decreased the force of potentiated contractions relative to control; and 4) increased the length of the period required for maximizing potentiated state contractions. They concluded from these observations that thiopental had two major effects on the contractile process: The first was to inhibit  $\text{Ca}^{2+}$  influx via the sarcolemma, and the second was to decrease the rate of movement of  $\text{Ca}^{2+}$  within the sarcoplasmic reticulum from uptake sites to release sites. They also concluded that thiopental had little effect on the total  $\text{Ca}^{2+}$  available within the sarcoplasmic reticulum. Our data, which reflect one aspect of SR function, the uptake process, support the findings of Komai and Rusy. Thiopental, at concentrations known to depress contractile activity, has essentially no effect on cardiac sarcoplasmic

reticulum  $\text{Ca}^{2+}$  uptake. The effect of thiopental on other sites of  $\text{Ca}^{2+}$  flux, such as the entry of  $\text{Ca}^{2+}$  through sarcolemmal, voltage-dependent  $\text{Ca}^{2+}$  channels needs to be examined to verify previous physiologic experiments.

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## Is Milrinone Equivalent to Amrinone during Enflurane Anesthesia in the Dog?

Virve H. M. Makela, MD, and Patricia A. Kapur, MD

MAKELA VHM, KAPUR PA. Is milrinone equivalent to amrinone during enflurane anesthesia in the dog? *Anesth Analg* 1988;67:349-55.

*Dose-response curves for milrinone during 2.1-2.3% end-tidal enflurane anesthesia were studied in six dogs given three successive boluses and 30-minute infusions of milrinone: 1) 40  $\mu\text{g/kg}$  plus 3  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (plasma level at 5 and 30 minutes after beginning of infusion:  $122 \pm 14$  and  $136 \pm 14$  ng/ml); 2) 60  $\mu\text{g/kg}$  plus 6  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  ( $285 \pm 31$  and  $304 \pm 19$  ng/ml); 3) 80  $\mu\text{g/kg}$  plus 12  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  ( $498 \pm 32$  and  $581 \pm 28$  ng/ml), demonstrating a progressive improvement of cardiac performance. Differences between milrinone and amrinone were also studied during enflurane anesthesia in six other dogs given milrinone or amrinone at 3- to 4-week intervals using both*

*a low dose that did not decrease mean arterial pressure significantly and a dose that decreased mean arterial pressure 20-25% below baseline values. There was a dose-related effect with both drugs on the measured hemodynamic variables. Plasma catecholamine levels did not change significantly in either group. The results of our studies show that during enflurane anesthesia 1) there is a correlation between milrinone plasma levels and improvement of cardiac performance and, 2) milrinone, at low and high doses studied without or with a significant decrease in mean arterial pressure, respectively, is similar to amrinone in its activity to improve cardiac performance by similar positive inotropic, chronotropic, and vasodilating effects.*

Key Words: ANESTHETICS, VOLATILE—enflurane. HEART, CONTRACTILITY—milrinone, amrinone. PHARMACOLOGY—milrinone, amrinone.

Milrinone, a methyl carbonitril derivative of amrinone, has been shown to improve cardiac performance in isolated animal hearts, and in animal studies with normal and failing hearts (1,2). Milrinone has also been shown to have favorable effects on cardiac performance in patients with congestive heart failure during either short- or long-term treatment and even during exercise in these patients (3-5). Milrinone, 15 to 30 times more potent than amrinone, is suitable both for intravenous use, as well as for long-term oral therapy with fewer side effects than amrinone (4,6). Approval is currently pending for clinical use of both formulations of milrinone in the United States.

In previous studies amrinone 1) improved cardiac performance in a dose-related fashion during inhalation anesthesia and, 2) was of therapeutic value for

the reversal of untoward effects of potent cardiodepressant drugs such as verapamil and propranolol, even in the presence of inhalation anesthetics (7-9). With higher doses of amrinone prominent findings in these studies were decreases in blood pressure and systemic vascular resistance associated with improved cardiac performance. Milrinone may supplant amrinone because unlike amrinone, after successful intravenous therapy with milrinone, patients can then be maintained on oral therapy. There are, however, no comparisons of milrinone and amrinone in the presence of anesthetics.

The purposes of the present study were 1) to establish a dose-response relation for milrinone during enflurane anesthesia and, 2) to determine if milrinone has cardiovascular effects different from those associated with amrinone during 2.1-2.2% end-tidal enflurane anesthesia when two different doses of milrinone or amrinone were administered: a low dose of milrinone or amrinone with no significant change in blood pressure and a high dose of milrinone or amrinone with a significant decrease in blood pressure.

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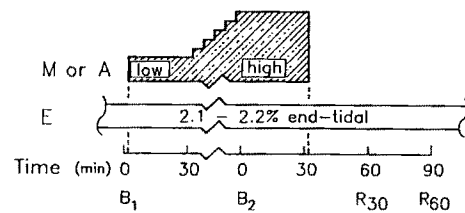
## Methods

The experimental protocol was approved by the Institutional Animal Research Committee. The animals were cared for in accordance with the American Association for Accreditation of Laboratory Animal Care.

All dogs were anesthetized with 2.1–2.3% end-tidal enflurane in 40% oxygen in air via a chronic tracheostomy and were mechanically ventilated (Harvard Apparatus Company model 623), to maintain  $P_{aCO_2}$  within normal limits as determined by serial arterial blood gas measurements every 30 minutes during each experiment (Instrumentation Laboratories Analyzer model 813).  $NaHCO_3$  was administered as needed to maintain pH within normal limits.  $NaCl$  0.9%, approximately  $10\text{ ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ , was infused intravenously to maintain adequate hydration and urine output. Temperature was maintained between 38 and 39°C with a warming blanket and a heating lamp. End-tidal concentrations of enflurane,  $CO_2$ , and  $O_2$  were continuously measured by mass spectrometry (Perkin-Elmer model MGA 1100). An arterial catheter was placed in a femoral artery for direct measurements of blood pressure and for blood sampling. A pulmonary artery catheter was passed via an external jugular vein for measurements of both right atrial, mean pulmonary artery, and pulmonary capillary wedge (PCWP) pressures and cardiac output (CO), the latter in triplicate by thermodilution (Edwards Laboratory Cardiac Output Computer model 9520). A micromanometer-tipped catheter (Millar Instruments, Inc. model PC 350) was placed retrogradely in the left ventricle (LV) via a femoral artery, for direct LV pressure measurements and electronic derivation of LV  $dp/dt$ . The maximum LV  $dp/dt$  (LV  $dp/dt_{max}$ ) was taken as the peak positive deflection of the LV  $dp/dt$  trace. Limb lead II of the ECG, heart rate (HR), arterial blood pressure, central venous pressure (CVP), pulmonary arterial pressure, LV pressure, and LV  $dp/dt$  were continuously recorded on a Hewlett-Packard polygraph model 7758A. In addition, the ECG was intermittently recorded at fast paper speed (100 mm/sec) for measurement of PR intervals. Systemic and pulmonary vascular resistances and cardiac, stroke volume, and stroke work indexes were calculated (SVR, PVR, CI, SVI, and SWI). The blood samples were analyzed for plasma concentrations of epinephrine (EPI), norepinephrine (NEPI), amrinone, and milrinone by high-performance liquid chromatography (10–12).

### Milrinone

The dose-related effects of milrinone were studied in



**Figure 1.** Experimental protocol for comparative part of the study. M or A, milrinone or amrinone administration. M: low dose =  $30\text{ }\mu\text{g}/\text{kg}$  plus  $3\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , high dose =  $60\text{ }\mu\text{g}/\text{kg}$  plus  $6\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  or higher (see text). A: low dose =  $2\text{ mg}/\text{kg}$  plus  $30\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , high dose =  $4\text{ mg}/\text{kg}$  plus  $100\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  or higher (see text). E, enflurane; B<sub>1</sub> and B<sub>2</sub>, baseline 1 and baseline 2 (see text); R<sub>30</sub> and R<sub>60</sub>, recovery, 30 and 60 minutes after cessation of drug infusions.

six conditioned mongrel dogs of either sex, weighing  $19 \pm 1\text{ kg}$  (mean  $\pm$  SEM). After instrumentation the dogs were allowed to stabilize with 2.2–2.3% end-tidal enflurane for 60 minutes. Baseline measurements and blood samples were then taken, after which each dog received the following successive loading doses (over 5 minutes) and 30-minute infusions of milrinone: M<sub>1</sub>,  $40\text{ }\mu\text{g}/\text{kg}$  plus  $3\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; M<sub>2</sub>,  $60\text{ }\mu\text{g}/\text{kg}$  plus  $6\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; and M<sub>3</sub>,  $80\text{ }\mu\text{g}/\text{kg}$  plus  $12\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . The cardiovascular measurements and blood samples were repeated 5, 25, and 30 minutes after beginning each 30-minute milrinone infusion and at recovery, 30 and 60 minutes after cessation of the milrinone infusion.

### Efficacy of Milrinone and Amrinone

The experiments to compare the efficacy of milrinone with amrinone were done in six other conditioned mongrel dogs given milrinone and amrinone (M and A groups). At 3- to 4-week intervals, each of the two experiments were carried out in these dogs of either sex, weighing  $18 \pm 1\text{ kg}$  (mean  $\pm$  SEM). After 60 minutes of stabilization with 2.1–2.2% end-tidal enflurane, baseline (B<sub>1</sub>) measurements were made and blood samples drawn (Fig. 1). Each experiment then consisted of two parts.

I. A low dose of milrinone or amrinone was first administered for 30 minutes at a fixed rate, as determined in this and previous studies (7,8) to investigate drug-related cardiovascular changes not associated with a significant decrease in blood pressure (decrease in MAP  $<6\%$  below B<sub>1</sub>). The loading doses and infusion rates were: milrinone  $30\text{ }\mu\text{g}/\text{kg}$  over 5 minutes followed by  $3\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; and amrinone  $2\text{ mg}/\text{kg}$  over 5 minutes followed by  $30\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . The loading dose of milrinone in this study was slightly less than the lowest one in the first part of the present study of the dose-related

effects of milrinone to keep any change in MAP under the limit desired in this part of the protocol. Measurements and blood samples were repeated 25 and 30 minutes after starting each drug administration.

II. High doses of milrinone or amrinone were then given at a rate that decreased the value of MAP 20–25% below  $B_1$ . The drugs were given as follows: for milrinone a second loading dose ( $60 \mu\text{g/kg}$ ) was given over 5 minutes and the infusion rate was initially increased to  $6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . The infusion rate was further increased by  $2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  every 15 minutes until the desired decrease in MAP was reached. The same procedure was followed for amrinone with a second loading dose of  $4 \text{ mg/kg}$ , an initial increase in infusion rate to  $100 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , and infusion increments of  $50 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . When the desired 20–25% decreases in MAP were achieved and had remained stable for 15 minutes for milrinone and amrinone, the hemodynamic measurements and blood samples were taken again serving as a second baseline ( $B_2$ ) for the high dose of milrinone and amrinone. The infusion rate of each drug was then kept unchanged for a 30-minute period, and hemodynamic measurements and blood samples were repeated 25 and 30 minutes after the beginning of this period. After these measurements the drug infusion was discontinued, and the measurements again repeated at recovery, 30 and 60 minutes after cessation of the milrinone or amrinone infusion.

In both studies, milrinone and amrinone were freshly prepared the day of the experiment. The milrinone solvent, the same as that used for amrinone, has been shown previously to have no statistically significant effect on hemodynamic parameters in a similar model in this laboratory (7,8).

Blood samples for measurements of serum levels of sodium, potassium, calcium, chloride, glucose, and hematocrit were taken three times during each experiment: at baseline ( $B$  or  $B_1$ ) for each studies; at the end of the  $M_2$  infusion in the dose-response study or at the second baseline ( $B_2$ ) in the comparative study; and when final cardiovascular measurements were made in both studies.

Statistical analysis was done by using analysis of variance for repeated measures for intragroup differences, and nonpaired  $t$ -tests in the comparative study. Bonferroni modified  $t$ -tests were used when analysis of variance for repeated measures indicated a significant difference. A  $P$  value of  $<0.05$  was considered statistically significant.

## Results

### *The Milrinone Dose-Response Study*

In the milrinone dose-response study there were no significant differences in hemodynamic function among the 5-, 25-, and 30-minute values of each of the three different 30-minute milrinone administration periods, except for CVP, which was lower at 25 minutes than that at 30 minutes during the  $M_1$  infusion. The enflurane end-tidal concentrations (2.2–2.3%) were stable over time in all dogs. The milrinone plasma levels were stable during each of the three different milrinone infusions, except during  $M_3$ , when the milrinone plasma level was significantly greater at 25 and 30 minutes than at 5 minutes. The hemodynamic values and catecholamine and milrinone plasma levels are shown in Table 1.

The  $M_1$  infusion, resulting in milrinone plasma levels of  $122 \pm 14$  to  $136 \pm 14 \text{ ng/ml}$  (5- and 30-minute values), increased LV  $\text{dP/dt}_{\text{max}}$  and CI above baseline values and decreased PCWP, CVP, SVR, MAP, and PR interval below baseline values. However, at 5 minutes of  $M_1$  the changes in MAP and PR interval were not yet statistically significant, and SWI and SVI were temporarily increased above baseline values. The  $M_2$  infusion, resulting in milrinone plasma levels of  $285 \pm 31$  to  $304 \pm 19 \text{ ng/ml}$ , further increased LV  $\text{dP/dt}_{\text{max}}$  and further decreased PCWP and, in addition, increased HR above baseline values. The  $M_3$  infusion, resulting in milrinone plasma levels of  $498 \pm 32$  to  $581 \pm 28 \text{ ng/ml}$ , further increased LV  $\text{dP/dt}_{\text{max}}$ . In addition,  $M_3$  also increased SVI above baseline values. There were significant increases in CI, LV  $\text{dP/dt}_{\text{max}}$ , and HR with decreases in PR interval and MAP with lower SVR when the values of  $M_3$  were compared to those of  $M_1$ . Thirty and 60 minutes after discontinuation of the milrinone infusions, with plasma levels of  $255 \pm 23 \text{ ng/ml}$  and  $161 \pm 9 \text{ ng/ml}$ , respectively, LV  $\text{dP/dt}_{\text{max}}$  and CI remained increased, whereas CVP, PCWP, MAP, and SVR were below baseline values. At 30 minutes of recovery, HR was still increased and PR interval shortened, but at 60 minutes HR was no longer different from baseline value, although PR interval remained shortened. At 30 and 60 minutes of recovery, milrinone plasma levels were similar to the levels associated with 30-minute administration of  $M_2$  and  $M_1$ , respectively. The differences in the hemodynamic values when the 30-minute values of  $M_1$  were compared to the 60-minute values of recovery, were not significant, nor were they significant when the 30-minute values of  $M_2$  were compared with the 30-minute values during recovery.

Table 1. Cardiovascular Values and Catecholamine and Milrinone Plasma Levels for Three Infusion Rates of Milrinone

	Baseline	Milrinone		
		$M_1:40 \mu\text{g/kg} + 3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$		$M_2:60 \mu\text{g/kg} + 6$
		5 min	30 min	5 min
HR (beats/min)	123 $\pm$ 5*	127 $\pm$ 7	135 $\pm$ 5	151 $\pm$ 6†
PR (msec)	114 $\pm$ 5	107 $\pm$ 6	101 $\pm$ 5†	96 $\pm$ 4†
MAP (mm Hg)	97 $\pm$ 6	89 $\pm$ 6	83 $\pm$ 5†	76 $\pm$ 5†
CVP (mm Hg)	3.1 $\pm$ 0.4	2.1 $\pm$ 0.4†	1.8 $\pm$ 0.4†	1.8 $\pm$ 0.4†
PCWP (mm Hg)	7.6 $\pm$ 0.5	4.9 $\pm$ 0.4†	4.5 $\pm$ 0.5†	3.5 $\pm$ 0.4†
LV dP/dt (mm Hg/sec)	1713 $\pm$ 109	3079 $\pm$ 172†	3033 $\pm$ 169†	3713 $\pm$ 163†
CI ( $\text{L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ )	4.3 $\pm$ 0.4	5.9 $\pm$ 0.9†	5.6 $\pm$ 0.8†	6.1 $\pm$ 0.9†
SVI ( $\text{ml}/\text{m}^2$ )	35 $\pm$ 2	47 $\pm$ 6†	41 $\pm$ 5	40 $\pm$ 5
SWI ( $\text{g}\cdot\text{m}\cdot\text{m}^{-2}$ )	41 $\pm$ 2	53 $\pm$ 6†	42 $\pm$ 3	38 $\pm$ 3
SVR ( $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$ )	2359 $\pm$ 331	1685 $\pm$ 312†	1669 $\pm$ 310†	1447 $\pm$ 307†
PVR ( $\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}$ )	159 $\pm$ 13	154 $\pm$ 16	154 $\pm$ 21	167 $\pm$ 25
EPI (pg/ml)	73 $\pm$ 22	101 $\pm$ 21	105 $\pm$ 25	109 $\pm$ 31
NEPI (pg/ml)	73 $\pm$ 16	60 $\pm$ 12	76 $\pm$ 17	67 $\pm$ 12
Milrinone (ng/ml)		122 $\pm$ 14	136 $\pm$ 14	285 $\pm$ 31

\*Mean  $\pm$  SEM;  $n = 6$  for each group.† $P < 0.05$  when compared with baseline value (30-minutes values for  $M_1$ ,  $M_2$ ,  $M_3$ ).‡ $P < 0.05$  when  $M_2$  was compared with  $M_1$ ,  $M_3$  with  $M_2$ ,  $R_{30 \text{ min}}$  with  $M_3$ , and  $R_{60 \text{ min}}$  with  $R_{30 \text{ min}}$  (30-minute values for  $M_1$ ,  $M_2$ , and  $M_3$ ).† $P < 0.05$  when  $M_3$  was compared with  $M_1$  (30-minute values).

### Differences between Milrinone and Amrinone

During the experiments to evaluate the differences between milrinone and amrinone the end-tidal enflurane concentrations (2.1–2.2%) remained stable over time in both groups with no significant differences between the two groups. There were no differences in any variable at the time of baseline ( $B_1$ ) measurements among groups M and A or among the 25- and 30-minute mean values for any variable in any group for any of the measurement periods, indicating a relatively stable condition at the time of the measurements. Thus the 30-minute values were used for statistical comparisons (Table 2).

The hemodynamic values, catecholamine levels, and plasma milrinone and amrinone levels for the M and A groups at  $B_1$  before the low dose, at  $B_2$  after achievement of the high dose, and at 30 minutes of the low and high doses as well as the 30- and 60-minute values of recovery are shown in Table 2. At 30 minutes with low doses of milrinone and amrinone the values of MAP were not significantly different from the corresponding  $B_1$  values. The high doses of milrinone or amrinone decreased MAP by 19% and 24%, respectively, at  $B_2$  compared to corresponding MAP values at  $B_1$ . The decreases in MAP were equivalent with both drugs and remained stable during the subsequent 30-minute drug infusion period.

**Low doses of milrinone or amrinone.** With both milrinone and amrinone, LV dP/dt<sub>max</sub> and SWI increased; CVP, PCWP, and SVR decreased; PR interval short-

ened and, in addition, CI, SVI, and HR increased above baseline levels in the M group. Milrinone and amrinone plasma levels at the end of this period were  $141 \pm 15$  ng/ml and  $2.8 \pm 0.2$   $\mu\text{g/ml}$ , respectively.

**High doses of milrinone or amrinone.** When  $B_2$  measurements were made with both milrinone and amrinone, after titration to a 19–24% decrease in MAP, LV dP/dt<sub>max</sub>, and HR had increased further, and PCWP had decreased further compared with levels seen with the low-dose infusion. Amrinone also further decreased SVR, further increased CI, and further shortened PR interval. After 30 minutes of the continued high-dose infusion these changes persisted except that PVR decreased below the original baseline level ( $B_1$ ) in the A group. The maximum infusion rate required for milrinone was  $8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in two of six dogs,  $10 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in two of six, and  $12 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in the remaining two dogs. The maximum infusion rate of amrinone was  $100 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in two of six dogs,  $150 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in two of six, and 200 and 250  $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  in the remaining two dogs. The plasma levels during the high-dose period ( $B_2$  and 30 minutes) were  $480 \pm 37$  and  $537 \pm 45$  ng/ml for milrinone, and  $12.8 \pm 1.4$  and  $14.4 \pm 2.1$   $\mu\text{g/ml}$  for amrinone.

Thirty minutes after cessation of the milrinone or amrinone infusions, LV dP/dt<sub>max</sub>, CI, SVI, and HR remained elevated, PR interval remained shortened, CVP and PCWP were still below  $B_1$  levels in both groups and, in addition, SWI remained higher in the



Table 1 (continued)

infusion			Recovery	
$\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$	$\text{M}_3:80 \mu\text{g}/\text{kg} + 12 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$			
30 min	5 min	30 min	30 min	60 min
149 $\pm$ 8†	163 $\pm$ 7†	161 $\pm$ 7†,‡	146 $\pm$ 7†	137 $\pm$ 8
94 $\pm$ 4†	92 $\pm$ 3†	91 $\pm$ 3†,‡	97 $\pm$ 3†	99 $\pm$ 7†
74 $\pm$ 4†	65 $\pm$ 2†	71 $\pm$ 3†,‡	77 $\pm$ 4†	83 $\pm$ 6†
1.5 $\pm$ 0.4†	1.3 $\pm$ 0.4†	1.4 $\pm$ 0.5†	1.1 $\pm$ 0.3†	1.3 $\pm$ 0.3†
3.2 $\pm$ 0.3†,§	3.5 $\pm$ 0.3†	3.6 $\pm$ 0.3†	3.5 $\pm$ 0.5†	3.7 $\pm$ 0.5†
3688 $\pm$ 172†,§	4333 $\pm$ 214†	4267 $\pm$ 149†,‡,§	3513 $\pm$ 195 †,§	3229 $\pm$ 196†
5.9 $\pm$ 0.9†	6.5 $\pm$ 1.1†	6.8 $\pm$ 1.0†,‡	5.8 $\pm$ 1.0†	5.4 $\pm$ 0.8†
39 $\pm$ 5	39 $\pm$ 6	42 $\pm$ 6†	40 $\pm$ 6	40 $\pm$ 6
37 $\pm$ 3	33 $\pm$ 4	38 $\pm$ 4	39 $\pm$ 5	42 $\pm$ 6
1430 $\pm$ 272†	1178 $\pm$ 223†	1185 $\pm$ 220†,‡	1542 $\pm$ 289†	1732 $\pm$ 300†
148 $\pm$ 20	141 $\pm$ 27	123 $\pm$ 18	130 $\pm$ 25	149 $\pm$ 26
97 $\pm$ 29	113 $\pm$ 32	141 $\pm$ 54	115 $\pm$ 47	88 $\pm$ 37
89 $\pm$ 17	97 $\pm$ 20	108 $\pm$ 20	102 $\pm$ 27	88 $\pm$ 22
304 $\pm$ 19§	498 $\pm$ 32	581 $\pm$ 28†,§	255 $\pm$ 23§	161 $\pm$ 9§

M group while PVR remained lower in the A group compared to B<sub>1</sub>. At this time MAP had returned to values comparable to B<sub>1</sub> in dogs given milrinone but remained below B<sub>1</sub> in dogs given amrinone. Plasma levels of milrinone and amrinone at this point were 224  $\pm$  23 ng/ml and 10.7  $\pm$  1.4  $\mu\text{g}/\text{ml}$ , respectively. At 60 minutes of recovery these changes were still present, except that SVI and SVR in the M group returned toward B<sub>1</sub> values. In the A group, MAP increased above the 30-minute recovery value but, with decreased SVR, was still below the B<sub>1</sub> level. Milrinone and amrinone plasma levels at this point were 138  $\pm$  17 ng/ml and 9.3  $\pm$  1.4  $\mu\text{g}/\text{ml}$ , respectively.

*Intergroup comparisons.* These showed that the M and A groups were similar at the time of the measurements, except that at 30 minutes of the low dose, LV dP/dt<sub>max</sub> was lower in the A group than in the M group, and at 60 minutes of recovery, LV dP/dt<sub>max</sub> was higher in the A group than in the M group.

In both studies, EPI and NEPI plasma levels were variable with no significant differences within or between groups. Values for serum sodium, potassium, calcium, chloride, glucose, hematocrit, and arterial blood gases remained within normal limits throughout the studies in all dogs. No arrhythmias or other evidence of toxicity of the drugs used were observed.

## Discussion

It has previously been shown that amrinone can improve the depressant effects of enflurane anesthe-

sia (7,8). The present study indicates that milrinone, in an appropriate dose, has equivalent properties including the propensity to elevate cardiac index without decreasing blood pressure.

Bipyridines, milrinone and amrinone, inhibit cardiac phosphodiesterase, the enzyme responsible for the degradation of cyclic AMP. Increased intracellular cyclic AMP levels result in increased calcium influx which appears to be a major mediator of the ultimate physiologic actions of the bipyridines. By this mechanism of action they could partly counteract the effects of inhalation anesthetics. The latter have been shown to cause a dose-dependent cardiac depression (13) by altering intracellular calcium homeostasis or by interfering with slow calcium channel function (14-16).

The plasma levels of milrinone obtained in first part of this study correspond to low therapeutic, therapeutic, and high therapeutic levels in humans. Baim et al. (3) reported that in patients with congestive heart failure (NYHA Class III and IV) favorable effects were obtained at plasma levels of approximately 200 ng/ml. They reported an increase in CI and LV dP/dt of 53 and 28%, respectively, and a 35% decrease in SVR associated with a decrease in filling pressures and a slight fall in arterial pressure at plasma levels of approximately 400 ng/ml in their patients during short-term intravenous therapy (3). During treatment, however, the plasma levels may vary significantly depending on differences in renal and hepatic perfusion in patients with congestive heart failure. In the present study in healthy dogs, milrinone plasma levels of approximately 130 ng/ml improved cardiac performance without an increase in HR, and plasma levels of approximately 300 and 540

Table 2. Cardiovascular Values in the Milrinone (M) and Amrinone (A) Groups

	Low dose		High dose		Recovery	
	B <sub>1</sub>	30 min	B <sub>2</sub>	30 min	30 min	60 min
HR (beats/min)						
M	105 ± 5*	119 ± 3†	133 ± 5†,‡	136 ± 4†	123 ± 4†,‡	116 ± 5†
A	103 ± 4	113 ± 3	133 ± 5†,‡	138 ± 3†	127 ± 5†,‡	119 ± 6†
PR (msec)						
M	118 ± 8	98 ± 4†	93 ± 4†	92 ± 5†	94 ± 4†	96 ± 4†
A	128 ± 5	106 ± 5†	90 ± 3†,‡	88 ± 3†	91 ± 4†	98 ± 6†,‡
MAP (mm Hg)						
M	81 ± 3	77 ± 4	67 ± 3†,‡	66 ± 3†	81 ± 4†	87 ± 4
A	86 ± 3	81 ± 2	67 ± 2†,‡	65 ± 3†	72 ± 3†	78 ± 4†
CVP (mm Hg)						
M	4 ± 1	2 ± 1†	1 ± 1†	1 ± 1†	2 ± 1†	2 ± 1†
A	4 ± 1	2 ± 1†	1 ± 1†	1 ± 1†	1 ± 1†	1 ± 1†
PCWP (mm Hg)						
M	8 ± 1	6 ± 1†	4 ± 1†,‡	4 ± 1†	5 ± 1†	5 ± 1†
A	7 ± 1	5 ± 1†	3 ± 1†,‡	3 ± 1†	3 ± 1†	4 ± 1†
LV dP/dt (mm Hg/sec)						
M	1450 ± 22	2738 ± 120†	3308 ± 178†,‡	3542 ± 164†	3027 ± 150†,‡	2667 ± 153†
A	1392 ± 97	2283 ± 148†,§	3429 ± 156†,‡	3608 ± 193†	3392 ± 165†	3317 ± 147†,§
CI (L·min <sup>-1</sup> ·m <sup>-2</sup> )						
M	3.7 ± 0.3	5.8 ± 0.5†	6.0 ± 0.5†	6.1 ± 0.7†	5.5 ± 0.5†	4.9 ± 0.3†
A	3.7 ± 0.5	5.0 ± 0.5	6.4 ± 0.6†,‡	7.1 ± 0.8†	6.0 ± 0.7†	5.7 ± 0.7†
SVI (ml/m <sup>2</sup> )						
M	36 ± 3	49 ± 3†	45 ± 3†	45 ± 4†	45 ± 3†	42 ± 2
A	36 ± 4	44 ± 4	48 ± 4†	52 ± 5†	47 ± 4†	47 ± 5†
SWI (g·m·m <sup>-2</sup> )						
M	35 ± 3	47 ± 4†	39 ± 3†	37 ± 4	47 ± 5†,‡	47 ± 3†
A	38 ± 5	46 ± 5†	42 ± 3	43 ± 3	44 ± 5	47 ± 4†
SVR (dynes·sec·cm <sup>-5</sup> )						
M	2248 ± 157	1412 ± 144†	1206 ± 116†	1118 ± 147†	1548 ± 91†	1877 ± 145
A	2480 ± 232	1716 ± 128†	1112 ± 101†,‡	991 ± 103†	1307 ± 141†	1570 ± 268†
PVR (dynes·sec·cm <sup>-5</sup> )						
M	161 ± 9	129 ± 9†	149 ± 15	150 ± 17	143 ± 16	151 ± 14
A	187 ± 19	166 ± 7	158 ± 13	148 ± 12†	154 ± 12†	162 ± 7
EPI (pg/ml)						
M	74 ± 40	54 ± 21	42 ± 13	70 ± 33	36 ± 10	36 ± 11
A	159 ± 104	114 ± 62	115 ± 67	98 ± 56	64 ± 38	50 ± 27
NEPI (pg/ml)						
M	122 ± 88	89 ± 58	69 ± 42	64 ± 25	56 ± 20	51 ± 20
A	35 ± 7	38 ± 6	43 ± 11	54 ± 10	51 ± 12	39 ± 7
Drug levels						
M (ng/ml)		141 ± 15	480 ± 37†,‡	537 ± 45†	224 ± 23†,‡	137 ± 17†
A (μg/ml)		2.8 ± 0.2	12.8 ± 1.4†,‡	14.4 ± 2.1†	10.7 ± 1.4†,‡	9.3 ± 1.4†

\*Mean ± SEM; n = 6 for each group.

†P < 0.05 compared with B<sub>1</sub> for that same group.

‡P &lt; 0.05 compared with previous value for that same group.

§P &lt; 0.05 compared with the M group at the same time.

ng/ml even further improved hemodynamic values with an increasing chronotropic effect. Mean arterial pressure decreased along with a decrease in SVR during all three infusion periods. After cessation of drug infusion, both MAP and SVR gradually increased but still remained below baseline values. The reduction in SVR, by decreasing systolic myocardial wall stress, may offset the increase in myocardial oxygen consumption that might be caused by increased contractility and heart rate. Monrad et al. (17,18) showed in patients with congestive heart failure that milrinone caused no change in myocardial

oxygen consumption and had a direct vasodilator action on the coronary circulation. A slight decrease in myocardial oxygen consumption has been shown in patients with congestive heart failure treated with amrinone (19,20).

The peak positive left ventricular dP/dt is, with cautious interpretation, commonly used for determination of myocardial contractility (21,22). Wallace et al. (21) showed in an anesthetized, areflexic canine model that an increase of left ventricular end diastolic pressure to 11 from 5 cm H<sub>2</sub>O increased LV dP/dt<sub>max</sub> to 3500 from 2200 mm Hg/sec and that an increase in

HR to 188 from 120 beats/min (50% increase) increased  $LV\ dp/dt_{max}$  to 2680 from 2050 mm Hg/sec. In the present study the increase in  $LV\ dp/dt_{max}$  most likely indicated an increase in contractility because it was associated with changes in LV filling pressure in the opposite direction with low and high doses of milrinone or amrinone, the increments in HR being only approximately 10%.

In part I of the comparative protocol in the present study, improvements in cardiac performance were seen in both the M and A groups without a significant decrease in blood pressure. In the second part of the comparative protocol, further improvements in cardiac performance were seen at higher plasma levels of milrinone and amrinone associated with equal decreases in blood pressure, the improvements in cardiac performance being similar with milrinone and amrinone during 2.1–2.2% enflurane anesthesia. The half-lives of these drugs after intravenous administration in healthy volunteers and in patients with congestive heart failure are 0.8 vs 2.3 hours (milrinone) and 2.6 vs 5.8 hours (amrinone), respectively (23), which accounts for the persistent salutary effects of both agents up to at least 1 hour after the end of the infusions in the present study.

The results of the present study show, first, that there is a correlation between milrinone plasma levels and improvement of cardiac performance in enflurane-anesthetized healthy dogs with progressive positive inotropic, chronotropic, and vasodilatory effects without significant changes in plasma catecholamine levels. Second, as with amrinone, improvements in cardiac performance with milrinone were associated with decreases in blood pressure during inhalation anesthesia. Third, the hemodynamic effects of milrinone and amrinone during 2.1–2.2% end-tidal enflurane anesthesia (approximately 1 MAC in dogs) at low and high doses resulting in no reduction or in approximately 20% reduction of mean arterial pressure, respectively, are similar in their ability to improve cardiac performance by similar positive inotropic, chronotropic, and vasodilating effects.

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## Skin Pulse Wave Monitoring during Lumbar Epidural and Spinal Anesthesia

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MEIJER J, de LANGE JJ, ROS HH. Skin pulse wave monitoring during lumbar epidural and spinal anesthesia. *Anesth Analg* 1988;67:356-9.

*The effectiveness of pulse wave monitoring of the big toes was compared with loss of cold discrimination to determine the onset of nerve blockade during lumbar epidural and spinal anesthesia. Forty-seven patients scheduled for elective urologic or lower extremity operations were assigned to one of three groups. Group 1 (15 patients) received epidural mepivacaine 1.5% with epinephrine; group 2 (12 patients),*

*epidural bupivacaine 0.5%, and group 3 (20 patients), spinal bupivacaine 0.5%. In the epidural groups, the mean time to onset of increases in pulse wave amplitude was less than half the mean time to onset of decrease in cold discrimination ( $P < 0.05$ ). In patients given spinal anesthesia, there was no significant difference. The pulse wave monitor seems to be a sensitive and objective detector of early anesthetic effect during spinal and epidural anesthesia.*

Key Words: ANESTHETIC TECHNIQUES—epidural, spinal.

Early clinical signs of the onset of epidural or spinal anesthesia include venodilation and increased skin temperature caused by blockade of preganglionic sympathetic B-fibers (1,2). These are followed by loss of pinprick sensation and cold discrimination (i.e., perception) reflecting A $\delta$  and C-fiber blockade (2). Before these signs, however, pedal warmth may be experienced by the patient as early as 30 seconds after lumbar subarachnoid injection of a local anesthetic. This has been ascribed to brief stimulation of nerve fibers involved in transmitting the sensation of warmth (3).

Testing temperature or pinprick discrimination is commonly used to determine the onset of regional anesthesia. However, these methods may give poor information in heavily sedated patients or where communication is difficult.

Many methods have been used to measure changes in skin blood flow and temperature secondary to sympathetic blockade. These include electronic skin temperature measurement, laser Doppler flowmetry (4), infrared thermography (5,6), and skin conductance response (7). Although all of these have

been used during spinal anesthesia, these methods are often not practical in daily clinical practice, because they are too complicated or need strictly controlled environmental conditions.

Pulse wave monitoring or plethysmography has proven to be useful in visualizing changes in skin blood flow due to sympathetic blockade (8,9). The pulse wave monitor is a noninvasive device and can be applied easily and rapidly. We investigated the effectiveness of pulse wave monitoring in determining the onset of nerve blockade during lumbar spinal and epidural anesthesia in relation to decreases in cold perception.

### Methods

The study protocol was approved by the ethical committee of our institution, and all patients gave informed verbal consent.

Three groups of patients were studied: group 1, epidural mepivacaine 1.5% with epinephrine 1:200,000; group 2, epidural bupivacaine 0.5%; and group 3, spinal bupivacaine 0.5%. Demographics of the groups are given in Table 1.

The choice of lumbar anesthetic technique and agent used depended on the type and expected duration of surgery and age of the patient. The types of operations were urologic and orthopedic procedures of the lower limbs as well as peripheral vascu-

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Table 1. Patient Demographics

	Group 1	Group 2	Group 3
Technique	Epidural	Epidural	Spinal
Local anesthetic	Mepivacaine	Bupivacaine	Bupivacaine
No. of patients*	15 (13)	12 (6)	20 (16)
Age (years)	39.0 ± 15.7† (19-68)	53.0 ± 17.6 (27-82)	57.3 ± 17.5 (37-83)
Height (cm)	179.9 ± 8.1 (160-190)	174.0 ± 10.2 (157-191)	172.0 ± 7.9 (158-184)
Weight (kg)	78.1 ± 12.1 (54-100)	74.1 ± 8.9 (60-93)	73.5 ± 12.9 (50-102)
Puncture site	L3 ± 0.5 (L3-L4)	L3 ± 0.9 (L2-L5)	L3 ± 0.8 (L2-L5)
Volume injected (ml)	18.9 ± 3.5 (12-24)	15.1 ± 2.9 (10-20)	3.5 ± 0.4 (3.0-4.0)

\*Number of males in parentheses.

†Values are means ± SD, with range in parentheses.

lar surgery. Excluded were patients with known contraindications to spinal or epidural anesthesia. For premedication, diazepam 5-10 mg was given orally 2 hours before the procedure.

On arrival of the patient in the induction room, blood pressure and pulse rate were measured, the ECG was monitored, and an IV infusion of 500 ml lactated Ringer's solution was started. In groups 1 and 2, epidural puncture was performed in the lateral decubitus position using the loss-of-resistance technique with normal saline in a smoothly running syringe of glass, attached to a 16-gauge Tuohy needle. An epidural catheter was advanced by 3-4 cm into the epidural space. After catheter fixation, the patient was placed in the supine position. Pulse wave monitors (Datascop, reflection method) were applied to the plantar surface of both big toes, using a Velcro band cuff. The signals were visualized on two Datascop P870 monitors and continuously registered on a Gould four-channel recorder, at a speed of 25 mm/min.

After obtaining a baseline recording, a test dose of the local anesthetic was injected through the catheter. After 3 minutes, the remainder of the dose, calculated for age in milliliters per segment (10), was given. After completing the injection, a small ice bag was lightly applied to the skin of both legs every 30 seconds in the dermatome corresponding to the puncture site. The patient was asked if there was any difference in cold sensation compared to the ipsilateral arm. Positive results were marked on the recorder paper. Sensory blockade was determined using the pinprick method. Recording of the pulse waves was continued until anesthesia was complete in the entire lower extremity.

Both the envelop curve of the pulse wave in the baseline recording and the envelop curve of the

increasing part are approximated by straight lines. The intersection of these lines is taken as the onset of the increase.

Differences in times in minutes between completion of injection and increase in the curves of the pulse waves and the times after which a decrease in cold perception occurred were determined from the recorder paper.

In group 3 spinal anesthesia was performed after the pulse wave monitors were attached to the big toes. The recording was made in the same way as described above and continued until satisfactory anesthesia was obtained. Spinal puncture was always performed in the sitting position, with the legs straight out forward on the table. A 22-gauge spinal needle was used and advanced until a free flow of spinal fluid was obtained. A volume of 3-4 ml isobaric bupivacaine 0.5% was then injected, and the patient was placed in the horizontal position after 2-3 minutes (11).

After puncture, pinprick sensation and cold perception were measured, and the results recorded as a function of time.

Pulse wave recordings and cold sensitivity tests were always compared on the same side. Because the measured and calculated times fit in a normal distribution (Wilk-Shapiro test), the Student's *t*-test for paired observations was applied. In evaluating the significance of differences between the times at which the pulse waves increased and the cold perception decreased, *P* values <0.05 were considered to represent statistical significance.

## Results

An example of a recording is shown in Figure 1. In Table 2 the mean times of onset of increases in pulse wave amplitude and decrements in cold perception, with standard deviations and ranges, are given for the three groups. Pinprick sensitivity was always still intact when a decrease in cold sensation was first noticed.

In groups 1 and 2, the mean time to onset of increases in pulse waves was less than half the mean time that the cold perception decreased (*P* < 0.05). Increases in the pulse wave amplitude always preceded decreases in cold perception in all patients. There was no significant difference in times and onset of loss of cold perception and increases in pulse wave amplitude in group 3.

Pulse wave increments and decrements in cold perception, with two exceptions, were always followed by development of levels of surgical anesthesia

Figure 1. Example of a pulse wave recording, made at a speed of 25 mm/min, during and after epidural injection of 1.5% mepivacaine with epinephrine. Volumes injected are given between the recordings made in the left (L) and right (R) big toe. L3; lumbar puncture level; (arrows) onset of decrease in cold perception by the patient.

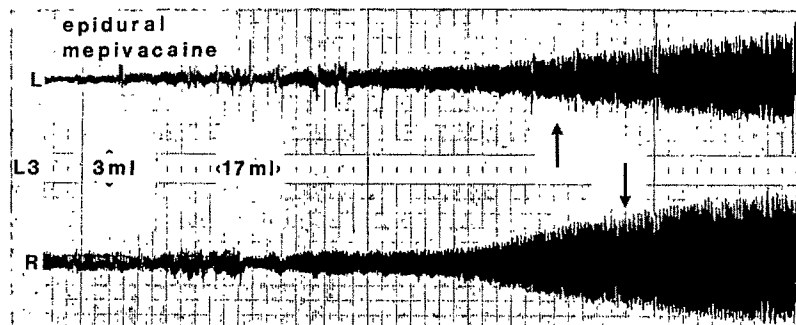


Table 2. Results of the Three Groups

Group	Time after Injection (min)			
	Left		Right	
	Increase Pulse Wave	Decrease Cold Sensitivity	Increase Pulse Wave	Decrease Cold Sensitivity
1	2.3 ± 1.3* (0.8-5.2) <i>P</i> < 0.05	4.7 ± 1.9 (1.9-8.8) <i>P</i> < 0.05	2.7 ± 1.5 (0.8-5.6) <i>P</i> < 0.05	5.4 ± 2.2 (1.9-9.0) <i>P</i> < 0.05
2	3.0 ± 2.6 (0.4-8.7) <i>P</i> < 0.05	5.8 ± 2.6 (2.0-9.9) <i>P</i> < 0.05	2.8 ± 2.5 (0.6-8.7) <i>P</i> < 0.05	5.5 ± 3.1 (2.0-13.1) <i>P</i> < 0.05
3	2.2 ± 1.4 (0.5-6.1) <i>P</i> = NS†	2.8 ± 1.3 (0.5-6.6) <i>P</i> = NS†	2.5 ± 1.6 (0.5-6.1) <i>P</i> = NS	2.6 ± 1.6 (0.5-6.6) <i>P</i> = NS

\*Values are means ± SD, with range in parentheses.

†Not significant.

adequate for urologic or lower extremity operations. In two patients, one in group 2 and one in group 3, there was a failure of regional anesthesia and general anesthesia was needed. In an additional patient in group 2 with adult-onset diabetes, cold discrimination decreased without any increase in the pulse wave amplitude, although operative anesthesia was satisfactory.

In patients in whom an asymmetrical increase in pulse waves was observed, the time at which cold perception decreased behaved in the same way. This is also illustrated in Figure 1. In some patients the level of sensory blockade that eventually developed was higher on the same side as that in which the pulse wave increased first.

## Discussion

The pulse wave monitor detects changes in light absorption due to alterations in skin capillary filling and transduces them electronically to a curve on a

monitor screen. Changes in distensibility of the vascular wall and in intravascular pulse pressure cause alterations in blood volume pulsations in the skin and so in the amplitude of the pulse wave. This peripheral arteriolar (and venular) wall distensibility is governed by the sympathetic nerve system, which controls smooth muscle fiber tone (12).

The skin of fingers, toes, and ear lobe is, in contrast to skeletal muscle, richly supplied with arteriovenous shunts; these do not exhibit basal tone and are almost exclusively under sympathetic control. These locations are most suitable for detection of amplitude changes of the pulse wave (9).

In our study only groups 2 and 3 can be compared with each other. Group 1 contained many young patients having ankle or knee operations, whereas in groups 2 and 3, the patients were older and were having urological or peripheral vascular operations. For orthopedic procedures, we prefer mepivacaine with epinephrine to bupivacaine, because we believe in superior analgesia with mepivacaine when low lumbar and sacral segments are to be blocked (13).

In groups 1 and 2, our findings show increases in onset of pulse wave amplitudes occurred more than twice as rapidly as did decreases in cold discrimination. The increase in the pulse wave is thus an early as well as an objective sign of local anesthetic effect at the puncture site and reflects a decrease of B-fiber activity. Cold discrimination requires patient cooperation and is more subjective.

In one case, regional anesthesia was preceded by a decrease in cold sensitivity only. This patient, who had mature onset diabetes for years, may have developed a polyneuropathy and a partial sympathectomy. Peripheral nerve disease may be a limiting factor for pulse wave monitoring of local anesthetic effects. On the other hand, all our patients with arteriosclerotic disease did show increases in the pulse waves, perhaps because pulse wave monitoring takes place primarily at the level of cutaneous capillaries.



In group 3 there was no significant difference between the mean times to changes in pulse wave amplitude and loss of cold discrimination. The patients in this group were sitting for the first few minutes, after having been lying down. This immediately causes a strong, general sympathetic reflex (14), possibly counteracting the start of sympathetic B-fiber blockade. Supine again, a sudden increase in the pulse waves always took place. As expected, spinal bupivacaine resulted in a more rapid onset of loss of cold perception than did epidural bupivacaine. On the other hand, the increase in pulse waves in the epidural group took place almost as rapidly as the increase in the spinal group. A recent study (15) demonstrated that sympathetic blockade during spinal anesthesia was less pronounced than with epidural anesthesia. The dilution of the small amount of local anesthetic injected in the spinal fluid may be an explanation. The larger mass of epidurally applied local anesthetic may cause relative early onset of B-fiber blockade.

In groups 1 and 2, the mean times in which the pulse waves increased after epidural mepivacaine with epinephrine did not differ significantly from those after epidural bupivacaine. Because of its physiochemical properties, we expected a slower onset of beginning of nerve fiber blockade by bupivacaine. We assume that the difference in age between these groups is compensated by the larger volume of local anesthetic used in the younger group 1. However, a statistical comparison between groups 1 and 2 could not be done.

In a previous study in which the pulse wave monitor was used for evaluation of chemical sympathectomy, changes in the pulse wave curve were found 3 to 5 minutes after block (9). Many of our results with spinal and epidural anesthesia are in the same range.

Obviously, we used the type of pulse wave monitor that was sensitive enough to detect increases in skin blood flow of the toes resulting from beginning B-fiber blockade during spinal or epidural anesthesia. We observed more rapid onset of increases in skin blood flow resulting from sympathetic blockade than decreases in cold and pinprick sensitivity during epidural anesthesia. This suggests that preganglionic B-fibers were blocked earlier than A $\delta$  and C-fibers.

Recent studies (5,7) reported that during spinal anesthesia the extent of sympathetic blockade was less than the extent of analgesia, leading to the conclusion that preganglionic B-fibers are more resistant to local anesthetics than are A-fibers. This is in

contradiction to our findings with epidural anesthesia.

In contrast, other investigators found a zone of differential sympathetic blockade six or seven spinal segments cephalad to the level of analgesia during spinal anesthesia (1,6). This agrees with our observation of easier blockade of sympathetic nerve fibers.

We conclude that during epidural anesthesia the pulse wave monitor is a simple, noninvasive, fast, and objective detector of early effects of the injected local anesthetic. The presence of peripheral nerve disease may limit its value. We also found evidence that, in vivo, the preganglionic sympathetic B-fibers may be more sensitive to epidurally injected mepivacaine and bupivacaine than are A $\delta$  and C-fibers.

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## In Vitro Cyanide Release from Sodium Nitroprusside in Various Intravenous Solutions

Shigemasa Ikeda, MD, Patricia A. Frank, BA, John F. Schweiss, MD, and Sharon M. Homan, PhD

IKEDA S, FRANK PA, SCHWEISS JF, HOMAN SM. In vitro cyanide release from sodium nitroprusside in various intravenous solutions. *Anesth Analg* 1988;67:360-2.

*The concentration of cyanide, a toxic metabolite of sodium nitroprusside, in solutions other than 5% dextrose in water, has not been reported. In this study, cyanide ion levels were measured by a cyanide ion-specific electrode in 250 ml of six different intravenous solutions (5% dextrose in water, 10% dextrose in water, distilled water, 0.9% sodium chloride, and lactated Ringer's solution with and without 5% dextrose) exposed to 300 foot candles of fluorescent light for 72 hours after sodium nitroprusside was dissolved in each solution. The rates of the increase in cyanide ion concentration in all six solutions were fairly constant between 4 and 24 hours. At 24 hours, there were*

*no statistically significant differences in cyanide ion concentration among the six solutions. After 24 hours, the rate of the increase in cyanide ion concentration in the electrolyte solutions decreased more than that in the nonelectrolyte solutions. At 72 hours, the electrolyte-containing solutions had statistically significant lower mean cyanide ion concentrations than 5% dextrose, often the recommended diluent for sodium nitroprusside. There was no difference in mean cyanide ion concentration between lactated Ringer's solution with and without 5% dextrose. Solutions containing electrolytes are preferable to 5% dextrose for the dilution of sodium nitroprusside.*

**Key Words:** ANESTHETIC TECHNIQUES, HYPOTENSIVE—nitroprusside. PHARMACOLOGY—nitroprusside.

The package insert for sodium nitroprusside states that sodium nitroprusside is only to be used as an infusion with 5% dextrose in water. Reasons for using only 5% dextrose in water are not mentioned in the package insert. A saline solution was used to mix sodium nitroprusside by Vesey et al. (1) in England, who mentioned neither the reasons nor the problems associated with using a saline solution.

Cyanide ion is released from sodium nitroprusside in vitro and in vivo. The cyanide ion concentration does not change over 72 hours in light-protected 5% dextrose in water solution (2). However, the concentration of cyanide ions released from sodium nitroprusside dissolved in other intravenous solutions has not been reported. The present study was performed

to measure the cyanide ion concentration in various intravenous solutions in which sodium nitroprusside was dissolved.

### Methods

Twenty-five milligrams of sodium nitroprusside powder was dissolved in 250 ml of each of the six different solutions in polyvinyl chloride bags. The solutions tested were: 1) 5% dextrose in water, 2) 10% dextrose in water, 3) distilled water, 4) 0.9% sodium chloride, and 5) lactated Ringer's with and without 5% dextrose. Five bags of each solution were exposed to 300 foot candles of fluorescent lamp throughout the 72-hour experiments without aluminum foil wrapping.

The cyanide ion concentration was measured directly by the cyanide ion-specific electrode (Orion Research Inc., Cambridge, MA) utilizing a model 94-06 pH meter. The sensitivity of the electrode is 0.026 to 260 ppm. The correlation coefficient was -0.998 when the electrode potentials of the cyanide electrode were measured in the solution containing 0.1 to 50 ppm of known cyanide ion (2). Measure-

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**Table 1.** Comparison of Cyanide Concentrations in Six Solutions across a 72-Hour Period\*

Time (hr)		D5W†	D10W†	DW†	NS†	LR†	LR/D5W†
4	X	0.160	0.190	0.130	0.113	0.179	0.177
	SD	0.004	0.018	0.016	0.008	0.016	0.010
8	X	0.287	0.304	0.337	0.313	0.429	0.225
	SD	0.095	0.125	0.033	0.016	0.100	0.067
24	X	3.66	2.08	2.47	2.08	1.85	1.17
	SD	1.07	0.52	0.24	0.32	0.26	0.12
48	X	6.06	4.09	5.35	3.56	1.49	1.06
	SD	0.41	0.19	0.18	0.48	0.05	0.61
72	X	9.12‡	7.36‡	7.47‡	4.57‡,§	1.91§	2.08§
	SD	2.25	1.08	0.27	0.28	0.22	0.19

\*CN<sup>-</sup> concentration (ppm) is expressed as mean (X) and standard deviation (SD).

†Abbreviations: D5W, 5% dextrose in water; D10W, 10% dextrose in water; DW, distilled water; NS, 0.9% sodium chloride; LR, lactated Ringer's; LR/D5W, lactated Ringer's with 5% dextrose in water.

‡Statistically significant difference when compared with same solution at 24 h.

§Statistically significant difference when compared with D5W at same time period.

ments were performed at 4, 8, 24, 48, and 72 hours after the sodium nitroprusside was dissolved in the solution. Sodium nitroprusside-containing solutions were stored and the measurements were performed at room temperature.

Both the absolute concentration and rate of change of cyanide ion concentration in six solutions were examined. Initially, mean cyanide ion concentrations were plotted against time on a semilogarithmic graph to assess the major times of change in cyanide ion concentration as well as to determine the rates of change in each solution.

Following the graphical analyses, a two-factor repeated measures analysis of variance (ANOVA) was employed to determine if there were statistically significant differences in mean cyanide ion concentrations in the various solutions or in the rate of change with time at 24 and 72 hours. These times represent when the rates of cyanide ion production change. Tukey's method of multiple comparison tests are used to make these post hoc pairwise comparisons: 1) cyanide ion concentration in 5% dextrose in water versus each of the other solutions at 24 and 72 hours, 2) cyanide ion concentration in normal saline versus lactated Ringer's with and without 5% dextrose in water at 24 and 72 hours, and, 3) cyanide ion concentration differences at 24 and 72 hours for each solution. A *P* value <0.05 is considered statistically significant.

## Results

The ANOVA results confirmed the existence of a statistically significant (*P* < 0.001) effect of solution type, time, and the interaction of time and solution type (i.e., different rates of cyanide ion release among

solutions). The Tukey comparisons indicated that 1) none of the solutions had statistically different means at 24 hours, lactated Ringer's, with and without 5% dextrose in water and normal saline had statistically lower mean cyanide ion concentrations than 5% dextrose in water at 72 hours; 2) lactated Ringer's with and without 5% dextrose in water did not have statistically lower mean cyanide ion concentrations than normal saline either at 24 or at 72 hours and, 3) distilled water, 5% dextrose in water, 10% dextrose in water, and normal saline had statistically higher levels of cyanide ion concentrations at 72 hours than at 24 hours (Table 1).

## Discussion

The decomposition of sodium nitroprusside in an aqueous solution is complex and varies depending on many factors. One of the factors influencing the cyanide ion release from sodium nitroprusside is the intensity and the wave length of the light source. Previous experimental results in our laboratory indicate that cyanide ion concentration does not change significantly over 72 hours in the light-protected 5% dextrose in water solutions either exposed to light or stored in a dark room (2). In the present experiment, to examine how the magnitude of cyanide ion release from sodium nitroprusside differs in different solutions, the sodium nitroprusside-containing solutions were exposed to light without any type of protection.

Distilled water, not a suitable intravenous solution, was included in the study for comparison with other solutions. The solutions tested have different pH, osmolarity, and electrolyte content. Cyanide ion concentrations were statistically lower in the electrolyte-containing solutions at 72 hours than in the



nonelectrolyte solutions. It is probable, although not substantiated in this experiment, that ions in the electrolyte-containing solutions form a barrier around nitroprusside and thus reduce degradation, and/or that the cations in the solutions combined with cyanide ion, effecting a lower free cyanide ion concentration in the electrolyte solutions as opposed to those in the nonelectrolyte solutions.

After 48 hours the cyanide ion concentration is greater in normal saline than in lactated Ringer's. Lactated Ringer's contains  $K^+$  and  $Ca^{2+}$  in addition to  $Na^+$ , the only cation in normal saline. Potassium and/or  $Ca^{2+}$  ions might have a higher affinity to cyanide ion than  $Na^+$ . The difference in cyanide ion concentration observed between normal saline and lactated Ringer's solutions might be due to differences in the electrolytes in the solution.

There was no difference in mean cyanide ion concentration between lactated Ringer's and lactated Ringer's in 5% dextrose in water. We assume that dextrose and/or osmolarity had little effect on releasing or conjugating with cyanide ions.

Callan found that tests of stability of sodium nitroprusside performed at the Abbott Laboratories in normal saline, 5% dextrose in water, 5% dextrose in 0.45% sodium chloride, and 5% dextrose in 0.225% sodium chloride indicated that sodium nitroprusside remained physically and chemically stable in solution for at least 24 hours if properly protected from light (Callan CM, Director, Medical Affairs Hospital Products Division, Abbott Laboratories, personal communication). She also found that 1) the use of sodium chloride as the diluent for sodium nitroprusside (Nitropress) is not listed in the Abbott Laboratories package enclosure because it could create problems for a patient with restricted sodium intake and, 2) the choice of diluents for use with sodium nitroprusside is primarily a medical issue rather than a stability concern (personal communication, CM Callan; see earlier).

In patients, cyanide ion concentration ranged from 189 to 210  $\mu g/100$  ml (1.91 to 2.13 ppm) in erythrocytes and from 2.53 to 3.09  $\mu g/100$  ml (0.025 to 0.031 ppm) in plasma in the presence of clinically evident tachyphylaxis during sodium nitroprusside infusion (3), and 0.5 mg% (5.06 ppm) in autopsy blood from

cyanide poisoning (4). The fatal plasma cyanide ion concentration appears to be between 10 and 20  $\mu mol/L$  (0.101 to 0.202 ppm) (5). Currently, it is recommended that sodium nitroprusside solutions not be used after 24 hours even if properly protected from light. In the study, cyanide ion concentrations ranged from 1.17 ppm in lactated Ringer's in 5% dextrose in water to 3.66 ppm in 5% dextrose in water at 24 hours when the sodium nitroprusside solutions were exposed to light (300 foot-candles). The cyanide ion concentration was only 0.530 ppm at 24 hours when sodium nitroprusside solutions were protected from light (2). Considering the infusion volume of sodium nitroprusside-containing solutions and dilution by circulating blood volume after infusion, in vitro cyanide ion concentration in the diluent solution will probably not play a major role in cyanide toxicity.

On the basis of the present in vitro study and a previously reported study of sodium nitroprusside stability (6), we conclude that solutions containing electrolytes are preferable to 5% dextrose in water for the dilution of sodium nitroprusside, especially when dextrose infusion is not medically desirable. We also emphasize that sodium nitroprusside-containing solutions should be as fresh as possible and protected from light.

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## Effects of Continuous Arteriovenous Hemofiltration on Cardiopulmonary Abnormalities during Anesthesia for Orthotopic Liver Transplantation

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TUMAN KJ, SPIESS BD, MCCARTHY RJ, LOGAS WG, WILLIAMS JW, SANKARY HN. Effects of continuous arteriovenous hemofiltration on cardiopulmonary abnormalities during anesthesia for orthotopic liver transplantation. *Anesth Analg* 1988;67:363-9.

*Orthotopic liver transplantation (OLT) often involves large blood loss and replacement, as well as administration of large amounts of blood products to correct coagulation defects. Renal free water excretion is often impaired in end-stage liver disease and not responsive to routine diuretic therapy, predisposing these patients to accumulation of extravascular lung water. The effects of the intraoperative use of continuous arteriovenous hemofiltration (CAVH) on*

*cardiopulmonary and oxygen transport variables were studied in ten patients during and 24 hours after OLT. CAVH prevented increases in pulmonary shunt fraction while decreasing PEEP and  $\text{FiO}_2$  requirements. Pulmonary compliance was significantly higher after operation in patients receiving CAVH. Before surgical dissection, hemodynamic effects of CAVH were minimal. Postoperatively, patients having CAVH had lower cardiac filling pressures and more normal systemic vascular resistance than did patients not having CAVH. These data suggest that CAVH may be a useful intraoperative technique for patients with impaired renal function undergoing liver transplantation.*

**Key Words:** LIVER—transplantation. ANESTHETIC TECHNIQUES—liver transplantation.

Patients undergoing orthotopic liver transplantation (OLT) often have multisystem diseases involving nearly every organ system, and their intraoperative management remains a difficult challenge for anesthesiologists (1). Operations of long duration, often coupled with massive blood loss and an ongoing coagulopathy, require administration of large volumes of blood, blood products, and other fluids (2). It is well known that even previously healthy patients who experience acute massive surgical trauma and hemorrhage have a tendency to develop an expanded interstitial fluid compartment, including both "third space losses" at the site of surgical trauma as well as increases in peripheral and pulmonary interstitial fluid. Low serum oncotic pressures, elevated circulating aldosterone and antidiuretic hormone levels,

and high portal and systemic venous pressures in patients with end-stage hepatic disease enhance the risks of developing pulmonary interstitial and even alveolar edema in these settings. Furthermore, many patients with end-stage liver disease have a reduced capacity to excrete free water because of abnormal renal function, ranging from mild degrees of impairment to severe hepatorenal syndrome (3). The use of packed red cells instead of whole blood, transfusion of blood products such as fresh frozen plasma, cryoprecipitate, and platelets only when specifically indicated by coagulation testing, and limiting crystalloid use to only maintain electrolyte, acid-base, and blood glucose homeostasis all help to minimize extra fluid delivered to the patient undergoing liver transplantation. Early intraoperative application of positive end-expiratory pressure (PEEP) may be necessary to improve pulmonary gas exchange in these patients. The use of low-dose dopamine ( $1-4 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) and diuretics may augment fluid removal if adequate renal function exists. However, many patients undergoing liver transplantation have impaired renal func-

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tion and do not respond adequately to these methods of diuresis.

Other methods of fluid removal in these patients include hemodialysis and peritoneal dialysis. Abdominal surgery makes peritoneal dialysis impossible during the intraoperative period and contraindicates its use postoperatively. Hemodialysis is not always feasible in the critically ill patient, because hypotension and vascular instability can occur and preclude fluid removal. In addition, marked fluctuations in serum pH, oxygen tensions, and electrolyte levels can occur and may not be well tolerated by unstable patients. The addition of anesthesia and major blood loss in an already critically ill patient precludes the use of hemodialysis techniques intraoperatively.

A new technique, continuous arteriovenous hemofiltration (CAVH) has recently been employed for treatment of fluid excess in situations in which neither hemodialysis nor peritoneal dialysis are possible (4). CAVH is simple to use and does not require complicated equipment or specially trained personnel. CAVH is an extracorporeal technique in which fluid, electrolytes, and small- to medium-sized molecules (MW <50,000 daltons) are removed from the patients by ultrafiltration. A small filter with a highly water-permeable membrane and modified hemodialysis blood lines are used but without the need for special access to the patient except for arterial and venous catheters. Large fluctuations in plasma electrolyte levels are not seen with CAVH, because all substances that cross the membrane have the same concentration in the hemofiltrate and plasma. The patient's own arterial-to-venous pressure gradient moves the blood through the extracorporeal circuit. CAVH offers the advantage of minimizing hemodynamic changes and has been shown to be useful in critically ill patients with hemodynamic instability (5). There have been no reports of the intraoperative use of CAVH. Because of the above considerations, we evaluated the use of intraoperative CAVH and its effects on cardiopulmonary dynamics intraoperatively and postoperatively in patients undergoing orthotopic liver transplantation.

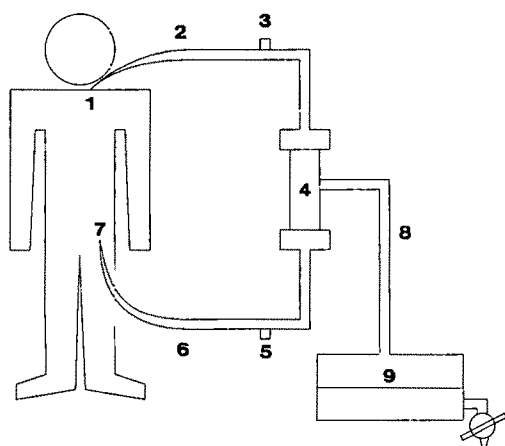
## Methods

Ten consecutive adult patients (age 17–57 years) undergoing orthotopic liver transplantation gave institutionally approved, informed consent. Five patients were selected to receive intraoperative CAVH because of poor renal function (creatinine clearance <45 ml/min). Anesthetic management was standardized as follows. After insertion of peripheral venous

and radial artery catheters, patients were preoxygenated for 3 minutes with 100% oxygen by mask. A rapid induction sequence using etomidate 0.3 mg/kg, fentanyl 100–200  $\mu$ g, succinylcholine 1.5 mg/kg, and cricoid pressure preceded oral endotracheal intubation. Anesthesia was maintained with isoflurane (0.25–2.0% end-tidal concentration) in O<sub>2</sub>/air with supplemental doses of fentanyl as needed; neuromuscular blockade was maintained with vecuronium. F<sub>IO<sub>2</sub></sub> was adjusted throughout the procedure as dictated by arterial oxygen saturation except during initial recirculation of the donor liver (portocaval anastomoses) when F<sub>IO<sub>2</sub></sub> was 1.0 until completion of the hepatic revascularization (hepatic artery). Positive end-expiratory pressure (PEEP) was applied as needed to maintain adequate arterial oxygen saturation at a nontoxic F<sub>IO<sub>2</sub></sub>. After induction of anesthesia, an oximetric/thermodilution pulmonary artery catheter was inserted and additional large-bore venous catheters were placed. Other monitors included a bladder temperature probe, pulse oximetry, and mass spectrometry as well as hourly urine output. Mixed venous (pulmonary arterial) blood samples were obtained to measure gas tensions and thus calibrate and verify accuracy of continuous mixed venous oximetry readings. A femoral arterial catheter (10-gauge) and a subclavian or internal jugular vein catheter (8.5F) were then placed and both cannulas attached to the inlet and outlet ports of the hemofilter using shortened hemodialysis blood lines previously flushed with heparinized saline. No other heparin was added to the system at any other time. The total amount of heparin that the patients were exposed to was 4–6 mg depending on the length of tubing used to connect the CAVH apparatus to the patient. The extracorporeal system (Fig. 1) consists of a small hollow fiber filter with a polysulfone membrane (model D30S, Amicon Corp., Lexington, MA). A side arm ultrafiltrate port drains to a graduated collection bag for measurement of ultrafiltrate volumes. The rate of ultrafiltrate formation is determined not only by hemofilter characteristics and the arterial–venous pressure gradient (and flow), but also can be regulated by changing the vertical distance between the collection bag and hemofilters (siphon effect) as well as by using variable partial occlusion of the ultrafiltrate line leading from the hemofilter to the collection bag.

Mixed venous oxygen saturations as well as arterial blood gas tensions were measured simultaneously with hemodynamic evaluations 20 minutes after insertion of monitoring lines and surgical incision but before institution of CAVH. These data were used to derive cardiac index (CI), systemic vascular





**Figure 1.** Continuous arteriovenous hemofiltration system for intraoperative use. 1, venous access; 2, venous line; 3, outlet sampling port; 4, hemofilter (Amicon D30S); 5, inlet sampling (and pressure monitoring) port; 6, arterial line; 7, arterial access; 8, ultrafiltrate line; 9, ultrafiltrate collection bag (see text for details).

resistance index (SVRI), and pulmonary vascular resistance index (PVRI) using standard formulas. Oxygen saturation, blood levels of carboxyhemoglobin and methemoglobin, as well as hemoglobin levels were measured with an oximeter (model 282, Instrumentation Laboratories, Lexington, MA). Oxygen extraction ratio  $[C(a-v)O_2/CaO_2]$ , arterial-venous oxygen content difference  $[C(a-v)O_2]$ , alveolar-arterial oxygen tension difference  $[P(A-a)O_2]$ , and pulmonary right-to-left shunt fractions ( $\dot{Q}_{sp}/\dot{Q}_t$ ) corrected for methemoglobin and carboxyhemoglobin (6) were calculated by standard formulas.

CAVH was then instituted and all of the above measurements were repeated at the following times in all patients: 5 minutes before inferior vena caval clamping (preanhepatic); 30 minutes after vena caval clamping (anhepatic); 30 minutes after reestablishment of vena caval flow (recirculation); 10 minutes before skin closure (end of case); and 24 hours postoperatively. All patients had femoral and portal vein to axillary vein bypass performed before caval clamping.

Intraoperative fluid therapy consisted of packed red cell and "cell saver" blood replacement, fresh frozen plasma, cryoprecipitate, and platelet infusions. Packed red cell therapy was guided by hemoglobin levels and hemodynamic data. All blood was administered through 20- $\mu$ m filters. Blood component therapy was guided by thrombelastography (7) as well as routine coagulation laboratory testing (PT, PTT, fibrinogen, and platelet counts). Crystalloid solutions were administered to supply  $Ca^{2+}$ ,  $HCO_3^-$ , and glucose. Postoperative intensive care procedures did not differ from well-established regimens. Cumulative volumes of fluid and blood products as well as

urine and ultrafiltrate volumes were noted at the above-measured times. Body weight was noted preoperatively, as well as on the first postoperative day. CAVH was continued into the postoperative period for variable periods depending on the clinical needs of the patient.

Data measured at repeated times in the same subject were analyzed for statistical significance of changes using a two-way analysis of variance with repeated measures in one variable. Post hoc tests were performed when appropriate using the Tukey-a method. Creatinine clearance, duration of surgery, 24 hour weight change, and cumulative fluid input/output were analyzed using the Student's *t*-test (pooled variance). The use of diuretics and renal dose dopamine was analyzed using Fisher's exact test.  $P < 0.05$  was considered statistically significant.

## Results

All patients were adults with end-stage hepatic failure and were classified as ASA physical status IVE. Four patients receiving CAVH had chronic active hepatitis and one had cryptogenic cirrhosis. The non-CAVH group comprised three patients with chronic active hepatitis, one with primary biliary cirrhosis and one with end-stage liver disease due to hemochromatosis. The average duration of anesthesia and surgery did not differ significantly between patients receiving and those not receiving CAVH ( $18.7 \pm 2.3$  vs  $18.4 \pm 2.7$  hours, respectively). Patients were selected to receive CAVH on the basis of poor preoperative renal function (creatinine clearance  $36.5 \pm 7.5$  vs  $56.3 \pm 9.6$  ml/min,  $P = 0.05$ ). There was no significant difference in preoperative diuretic use between the two groups (two of five without CAVH, zero of five with CAVH). Both groups displayed a statistically similar baseline hyperdynamic circulatory pattern typical of end-stage liver disease: high CI, elevated filling pressures, and low SVRI (Table 1). Peripheral oxygen extraction was reduced in both groups as reflected by low  $C(a-v)O_2$  and  $O_2$  extraction ratios. The groups did not have baseline differences in  $P(A-a)O_2$  or  $\dot{Q}_{sp}/\dot{Q}_t$ .

Hemodynamic and oxygen utilization effects of CAVH are summarized in Table 1. The progressive decline in CI in both groups was initially associated with interruption of inferior vena caval flow (albeit partially compensated by veno-veno-bypass, see earlier) and later with establishment of perfusion to the donor liver. SVRI increased gradually after the liver was replaced, perhaps due to closure of abnormal arteriovenous channels as well as a decrease in circu-

Table 1. Hemodynamic and Oxygen Utilization Effects of CAVH during Liver Transplantation

	Induction		Dissection		Anhepatic
	No CAVH	CAVH	No CAVH	CAVH	No CAVH
HR (beats/min)	87 ± 6*	88 ± 8	89 ± 4	88 ± 11	91 ± 8
PCWP (mm Hg)	14 ± 4	17 ± 6	16 ± 2	17 ± 6	14 ± 3
RAP (mm Hg)	13 ± 4	14 ± 4	14 ± 4	14 ± 4	10 ± 1
PAP (mm Hg)	24 ± 3	26 ± 5	24 ± 1	25 ± 5	22 ± 2
MAP (mm Hg)	81 ± 10	92 ± 5	78 ± 9	91 ± 6	83 ± 9
CI (L·min <sup>-1</sup> ·m <sup>-2</sup> )	4.9 ± 1.0	5.2 ± 0.3	4.9 ± 0.7	5.2 ± 0.3	4.4 ± 0.8
SVRI (dynes·sec·cm <sup>-5</sup> ·m <sup>-2</sup> )	1120 ± 120	1193 ± 138	1045 ± 129	1192 ± 131	1339 ± 212
PVRI (dynes·sec·cm <sup>-5</sup> ·m <sup>-2</sup> )	157 ± 52	136 ± 40	133 ± 56	136 ± 32	139 ± 87
C(a-v)O <sub>2</sub> (ml/dl)	2.95 ± 0.32	2.88 ± 0.18	2.94 ± 0.24	2.94 ± 0.22	3.02 ± 0.47
O <sub>2</sub> extraction ratio (%)	21.1 ± 4.0	20.8 ± 0.6	18.4 ± 1.4	20.3 ± 1.3	19 ± 3.6

\*Values are means ± SD.

†P &lt; 0.05 compared to no CAVH.

Abbreviations: HR, heart rate; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; PAP, pulmonary arterial pressure; MAP, mean arterial pressure; CI, cardiac index; SVRI, systemic vascular resistance index; PVRI, pulmonary vascular resistance index; C(a-v)O<sub>2</sub>, arterial-venous oxygen content difference.

lating humoral mediators of the hyperdynamic state. The increase in SVRI was statistically greater at the end of operation and 24 hours postoperatively in patients receiving CAVH. Elevated pulmonary artery pressures, combined with massive transfusions, resulted in significant elevation of RA pressure after revascularization of the liver in the patients without CAVH. Patients who received CAVH had significantly lower RAP and PCWP after recirculation, at the end of surgery and 24 hours postoperatively. The C(a-v)O<sub>2</sub> and O<sub>2</sub> extraction ratios were significantly increased after transplantation in patients receiving CAVH, indicating increased oxygen utilization by varicous body tissues.

The significantly lower cardiac filling pressures after recirculation in the patients receiving CAVH were accompanied by improved oxygen diffusion in the lung as reflected by a significantly decreased (P(A-a)O<sub>2</sub> and  $\dot{Q}_{sp}/\dot{Q}_t$  as well as lower FIO<sub>2</sub> and PEEP requirements compared to patients not having CAVH (Table 2 and Fig. 2). In addition, lung-thorax compliance was better at end of operation and 24 hours later in patients receiving CAVH (Table 2).

During the operative period, transfusion of blood (19.7 ± 3.5 vs 21.6 ± 8.7 L), blood products (28.9 ± 9.7 vs 30.2 ± 14.0 L), and crystalloid (6.4 ± 1.6 vs 5.8 ± 0.9 L) were not significantly different in patients without and with CAVH, respectively. Although blood loss could not be accurately quantified because it was so massive, adequacy and necessity of infusions used are demonstrated by maintenance of acceptable hematologic and electrolyte values in both groups (Table 2). Patients receiving CAVH produced significantly less urine than did patients not receiving CAVH: 32 ± 4 ml/hr vs 116 ± 11 ml/hr during surgery and 29 ± 4 ml/hr vs 55 ± 5 ml/hr in the first 24

postoperative hours. The average amount of hemo-filtrate removed intraoperatively was 694 ± 141 ml/hr and 431 ± 122 ml/hr during the first 24 postoperative hours. Hence, the total free water excretion of patients receiving CAVH was significantly greater than that in those not receiving CAVH. This removal of fluid was associated with a net decrease below pre-operative body weight (-4.1 ± 2.7 kg) in the patients receiving CAVH compared to a net increase (5.8 ± 1.5 kg) without CAVH, a statistically significant difference. None of the CAVH patients received intraoperative loop diuretics, but all of the patients without CAVH required diuretics intraoperatively, a statistically significant difference. The use of low dose dopamine for augmentation of urine output was not significantly different between groups (four of five without CAVH versus three of five with CAVH).

No complications were associated with the use of CAVH except for an inguinal hematoma in one patient, probably related to technical errors, coagulopathy, and arteriosclerotic vascular disease. Although the CAVH apparatus requires initial priming with heparinized saline (10 mg/L), we did not observe any significant additional bleeding problems in patients receiving CAVH, despite an already impaired coagulation system from end-stage liver disease. This may be because the amount of heparin is relatively small (the CAVH apparatus is minimally thrombogenic as long as continuous flow is maintained) and rapidly lost in the massive blood loss and replacement.

## Discussion

Acute pulmonary dysfunction after liver transplantation is not uncommon when blood losses necessitate

Table 1 (continued)

Anhepatic	Recirculation		End of procedure		24 hr Postoperative	
CAVH	No CAVH	CAVH	No CAVH	CAVH	No CAVH	CAVH
93 ± 13	95 ± 9	93 ± 14	100 ± 10	95 ± 15	97 ± 8	95 ± 12
15 ± 6	24 ± 6	18 ± 5†	23 ± 4	16 ± 3†	20 ± 3	16 ± 3
14 ± 4	19 ± 3	14 ± 4†	22 ± 4	14 ± 3†	18 ± 2	13 ± 2†
25 ± 3	33 ± 3	29 ± 2	32 ± 8	26 ± 3	30 ± 7	25 ± 4
80 ± 10	84 ± 8	92 ± 16	88 ± 4	93 ± 17	84 ± 3	99 ± 10
4.8 ± 0.2	4.2 ± 0.6	4.6 ± 0.5	4.2 ± 0.5	4.4 ± 0.5†	4.4 ± 0.4	4.0 ± 0.2
1102 ± 156†	1234 ± 46	1370 ± 304	1270 ± 195	1461 ± 256	1203 ± 119	1707 ± 128†
161 ± 51	204 ± 62	181 ± 50	194 ± 74	164 ± 111	191 ± 94	174 ± 100
3.13 ± 0.19	3.47 ± 0.44	3.68 ± 0.45	3.54 ± 0.34	4.54 ± 0.47†	3.42 ± 0.31	4.55 ± 0.35†
21.1 ± 2.6	24 ± 2.7	25.1 ± 3.1	22.5 ± 1.9	32 ± 3.1†	22.7 ± 2.0	31.8 ± 1.0†

Table 2. Pulmonary and Blood Value Measurements before and after Liver Transplantation

	Induction		End of procedure		24 hr postoperative	
	No CAVH	CAVH	No CAVH	CAVH	No CAVH	CAVH
P(A-a)O <sub>2</sub> (mm Hg)	129 ± 4	137 ± 21	361 ± 91	127 ± 24†	327 ± 89	122 ± 16†
Q <sub>sp</sub> /Q <sub>t</sub> (%)	11.2 ± 0.8	11.8 ± 1.6	24.2 ± 5.1	11.4 ± 3.1†	23.0 ± 4.9	10.6 ± 2.7†
PEEP (cm H <sub>2</sub> O)	0	0	12.0 ± 3.3	5 ± 0†	12.5 ± 3.5	4.0 ± 2.2†
Compliance (ml/cm H <sub>2</sub> O)	‡	‡	26.7 ± 15.3	53.6 ± 3.6†	30.5 ± 18.7	52.0 ± 2.3†
FiO <sub>2</sub>	0.5 ± 0	0.5 ± 0	0.7 ± 0.14	0.5 ± 0†	0.58 ± 0.8	0.50 ± 0†
Hemoglobin (g%)	10.5 ± 1.6	10.2 ± 0.4	11.5 ± 0.4	10.9 ± 0.9	10.9 ± 0.4	10.8 ± 0.5
Ca <sup>2+</sup> (mmol/L)	1.05 ± 0.07	1.04 ± 0.05	1.42 ± 0.04	1.36 ± 0.11	1.34 ± 0.08	1.34 ± 0.07
K <sup>+</sup> (meq/L)	4.0 ± 0.6	3.7 ± 0.3	3.6 ± 0.4	3.5 ± 0.3	3.8 ± 0.2	3.9 ± 0.2
Prothrombin time (%)	24 ± 17	32 ± 28	44 ± 10	45 ± 4	38 ± 4	41 ± 5
Fibrinogen (mg%)	176 ± 71	281 ± 157†	223 ± 39	301 ± 38†	230 ± 14	264 ± 42†
Platelet count (10 <sup>3</sup> /mm <sup>3</sup> )	96 ± 33	98 ± 65	111 ± 25	127 ± 21	81 ± 43	109 ± 13

\*Values are means ± SD.

†P &lt; 0.05 compared to no CAVH.

‡Not measured.

Abbreviations: CAVH, continuous arteriovenous hemofiltration; P(A-a)O<sub>2</sub>, alveolar-arterial oxygen tension difference; Q<sub>sp</sub>/Q<sub>t</sub>, pulmonary right-to-left shunt fraction; PEEP, positive end-expiratory pressure; FiO<sub>2</sub>, fraction of inspired oxygen.

transfusion of massive amounts of blood and blood products. Despite the use of blood filters, such massive transfusions may result in embolization of microaggregates to the pulmonary capillary bed (8,9). In addition, impaired cardiac function as well as increased pulmonary artery pressures and pulmonary vascular resistance may occur after recirculation of the transplanted liver (1,10). Backward cardiac failure may result in volume and pressure overload of the pulmonary venous system and increased pulmonary arterial pressures with pulmonary vasoconstriction. This can cause microcirculatory defects in the lung that may lead to increased capillary permeability (11). This abnormality is enhanced by low serum oncotic pressure, elevated venous pressures, impaired renal free water excretion in patients with end-stage hepatic disease, as well as postoperative right hemidiaphragm dysfunction. These factors often result in a combination of hydrostatic and nonhydrostatic pulmonary edema with resultant right-to-left intrapulmonary shunting and the need for extended supportive respiratory care (12).

In addition, a large spectrum of pathologic pulmonary conditions are associated with chronic liver disease, many resulting in arterial hypoxemia. Pathophysiologic pulmonary findings associated with end-stage hepatic disease include intrapulmonary, portopulmonary and pleural shunting, pulmonary hypertension, pleural effusions, impaired hypoxic vasoconstriction, nonspecific interstitial pneumonitis, low diffusing capacities, and increased closing capacity with premature airway closure (12). In view of the above, patients undergoing liver transplantation are at high risk for pulmonary complications. Although common causes of early postoperative mortality include surgical complications, graft rejection, and unsatisfactory grafts, pulmonary complications still contribute to considerable morbidity (12).

By using CAVH intraoperatively we were able to reduce right-to-left Q<sub>sp</sub>/Q<sub>t</sub>, improve oxygenation, and decrease PEEP requirements without adverse hemodynamic effects during anesthesia for liver transplantation. Reductions in PEEP requirements are beneficial, because impairment of venous return



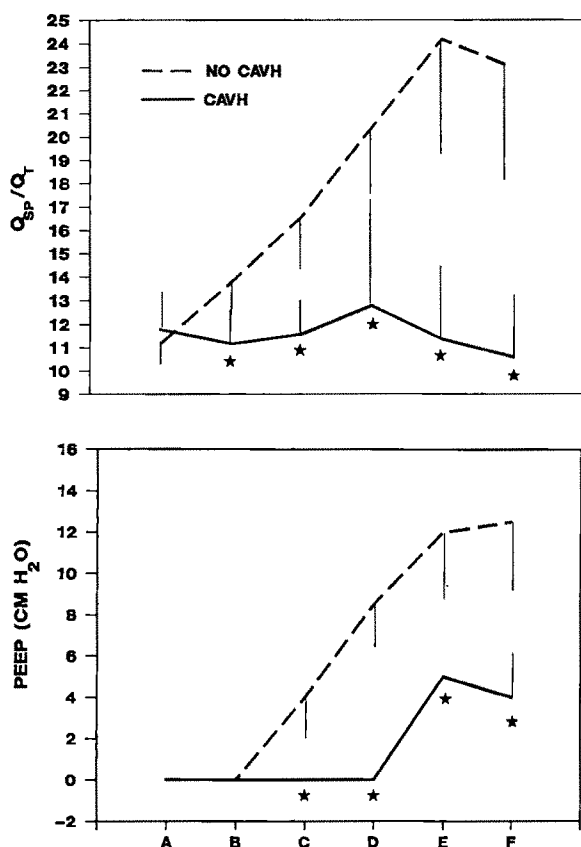


Figure 2. Changes in pulmonary shunt fraction and PEEP requirements during liver transplantation. Means  $\pm$  SD.  $\star$ ,  $P < 0.05$  for differences between the two groups. A, induction; B, dissection; C, anhepatic phase; D, recirculation; E, end of procedure; F, 24 hours postoperatively.

by PEEP may lead to hepatic congestion and reduce hepatic blood flow. For comparable transfusion needs, patients who received CAVH had significantly lower left- and right-sided filling pressures after recirculation and at the end of the procedure compared to those who did not receive CAVH. The improvements in  $Q_{sp}/Q_t$  and  $P(A-a)O_2$  as well as lung-thorax compliance are most likely due to decreased pulmonary interstitial edema because of the removal of excess free water by CAVH. In addition, CAVH increases colloid osmotic pressure (13) and theoretically should help draw extravascular water into the intravascular spaces, thus reducing extravascular lung water.

In this study, the selection of patients was biased against CAVH. Patients with poor renal function (i.e., those who received CAVH) have less ability than those with better renal function to excrete free water loads such as those they are exposed to during liver transplantation and thus would be predicted to have greater fluid retention, weight gain, and interstitial edema for comparable blood loss and fluid replacement. CAVH allows for excretion of free water

in considerable excess of that allowable by more normal renal function during liver transplantation, as is seen by comparing the total free water excretion in those patients who did to those who did not receive CAVH. Although CAVH appears to be useful as an "auxiliary kidney" in removing free water in patients with poor renal function under going liver transplantation, it must be noted that these results were obtained in a series of patients selected to receive or not receive CAVH based on preoperative renal status, rather than a randomized, blinded study.

In summary, CAVH appears to be associated with improved respiratory and hemodynamic function during and after anesthesia for orthotopic hepatic transplantation. We encountered no untoward hemodynamic responses despite intraoperative removal of many liters of fluid. Continuous arteriovenous hemofiltration (CAVH) is a simple technique that can be used by the anesthesiologist in the critically ill patient with impaired renal function even during the intraoperative period when effects of blood loss and anesthesia would make other alternatives to fluid removal, e.g., hemodialysis, unusable. The ease of establishing access to the patient for CAVH and the lack of need for special equipment or personnel allows rapid institution of this therapy and makes it a useful intraoperative technique that can easily be extended to the postoperative period. CAVH might also be useful in other intraoperative situations in which removal of excess fluid would be desirable (e.g., cases of massive blood loss and fluid replacement other than OLT in which pulmonary edema develops intraoperatively and conventional methods of diuresis are not applicable because of abnormal renal function, etc.). These preliminary results with intraoperative CAVH are encouraging and suggest the need for further clinical investigation.

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## Combined Intrathecal Morphine and Bupivacaine for Cesarean Section

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ABOULEISH E, RAWAL N, FALLON K, HERNANDEZ D. Combined intrathecal morphine and bupivacaine for cesarean section. *Anesth Analg* 1988;67:370-4.

*The effects of adding 0.2 mg preservative-free morphine sulfate in 0.2 ml solution to hyperbaric spinal bupivacaine were evaluated in a double-blind randomized prospective study of 34 patients undergoing elective repeat cesarean section. In the control patients (n = 17), 0.2 ml saline instead of morphine was added to bupivacaine. The intrathecal morphine significantly improved intra- and postoperative analgesia, e.g., 82% of patients given morphine compared with 41% of the control patients did not require analgesic supplementation to the spinal anesthesia during*

*surgery; postoperatively, the former patients did not request additional analgesia for  $27 \pm 0.7$  hours (mean  $\pm$  SEM) compared with  $2 \pm 0.3$  hours in the control patients. Neonatal condition was not adversely affected by this small dose of morphine administered  $11 \pm 1$  minutes before delivery. Combining 0.2 mg morphine with hyperbaric spinal bupivacaine for cesarean section is a safe and effective method of improving intraoperative pain relief and providing adequate prolonged postoperative analgesia.*

**Key Words:** ANESTHESIA—obstetric.  
ANESTHETIC TECHNIQUES, EPIDURAL—  
morphine.

Narcotics injected about the spinal cord have been used successfully for relief of pain in obstetrics. For example, epidural narcotics have been used in combination with local anesthetics for perioperative analgesia in cesarean section (1,2). Intrathecal morphine has also been used to produce analgesia during the first stage of labor (3-5). The addition of morphine to hyperbaric spinal bupivacaine would appear ideal for perioperative analgesia in cesarean section for the following reasons. First, it would be simple to do because both drugs would be injected simultaneously with one dural puncture. Second, it might be safer than epidural morphine if one considers the possibility of subdural or subarachnoid migration of the epidural catheter, the latter with the risk of injection of dosages adequate to produce respiratory depression (6). Third, a single small dose of intrathecal morphine may relieve the postoperative pain of a

lower abdominal operation such as a cesarean section. Intrathecal injection of 1 mg morphine carries a serious risk of respiratory depression (7) and, in a retrospective survey, even 0.3 mg subarachnoid morphine carries this risk (8); accordingly, we arbitrarily chose 0.2 mg morphine sulfate to supplement spinal bupivacaine.

The following double-blind randomized study was designed to evaluate the effect of such a small dose of morphine added to hyperbaric spinal bupivacaine for cesarean section. The intra- and postoperative analgesia and side effects were evaluated, and respiratory function was monitored for 24 hours using pulse oximetry.

### Methods

The study was approved by the Human Protection Committees of the University of Texas and Hermann Hospital at Houston. The study consisted of 34 full-term patients, without maternal or fetal compromise, scheduled for elective repeat cesarean sections performed before the onset of labor at 38 to 40 weeks gestation. The patient's written informed consent was obtained before participation. The patients were

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randomly classified into two groups of 17 each. In the study group, 0.2 mg preservative-free morphine sulfate in 0.2 ml solution (Duramorph, A.H. Robins Co.) was added to the hyperbaric bupivacaine just before the intrathecal injection, whereas in the control group 0.2 ml saline was added instead. The patient as well as the personnel collecting the data and evaluating the technique, namely, the anesthesiologist, the neonatologist, and the nurses, were unaware of the nature of the injectate.

The dose of hyperbaric bupivacaine, based on the patient's height (9), was 8.25 mg of 0.75% bupivacaine in 8.25% dextrose for 150 cm of height. The dose was increased or decreased by 0.75 mg bupivacaine (0.1 ml) for each 7.5 cm above or below 150 cm. No premedication was administered. The spinal anesthetic technique was the same in all patients. Lactated Ringer's solution 15 ml/kg was infused IV over 20 minutes before intrathecal injection of the drugs. Spinal anesthesia was induced with the patient in the right lateral horizontal position. Lumbar puncture was performed at the L2-3 interspace using a 26-gauge spinal needle. Free flow of clear cerebrospinal fluid before and after the injection was obtained. The intrathecal injection was completed in 10 seconds. Immediately after the injection, the patient was gently turned to the supine, horizontal position, which was maintained for at least 20 minutes. Left uterine displacement was accomplished using an air bag (10).

Intra- and postoperative arterial blood pressure and heart rate were monitored noninvasively, the former using an automatic oscillotonometric device (Dinamap), the latter using a precordial stethoscope, ECG, and/or pulse oximeter. Respiration was monitored by counting the respiratory rate, observing the patient's color, and determining the percentage of oxygen saturation of hemoglobin ( $\text{Sao}_2\%$ ) using a pulse oximeter (Novamatrix model 500). Although all patients were monitored by pulse oximetry, actual strip recording of pulse rate,  $\text{Sao}_2\%$ , and the total histogram of the collected trends data (Novagraph 312 by Novamatrix) became available during the latter part of the study in 17 patients. The total histogram was printed for pulse rate and  $\text{Sao}_2\%$  (trends 1 and 2). The histogram showed the total time the patient had been monitored and bar graphs represented the times spent at each range, e.g., with  $\text{Sao}_2\%$ , how many minutes at each range of 100-95, 95-90, 90-85% saturation, etc. The histogram also listed the number of events that occurred at each particular range and the longest duration of an event in each range. Therefore, not only respiratory depression, but its duration and frequency of recurrence could be easily

identified. The state of consciousness was graded as 1 (alert), 2 (sleepy but easily aroused), 3 (sleepy but aroused by painful stimuli), and 4 (comatose). The above data were recorded every minute until delivery, every 5 minutes until the end of surgery, every 15 minutes in the recovery room, and every hour for 24 hours in the patient's postpartum room. The narcotic requirement during the total hospital stay was also determined.

Hypotension was defined as a 20% decrease in systolic blood pressure. Ephedrine, injected in 10-mg increments, was used to correct maternal hypotension. Respiratory depression was defined as a respiratory rate of 10 breaths/min, cyanosis, and/or  $\text{Sao}_2 \leq 85\%$ . Intravenous naloxone in 0.1-mg increments was used for treatment of respiratory depression, CNS depression (a score of  $\geq 3$ ), and disturbing degrees of nausea, vomiting, or pruritus.

The criterion for administering a supplementary narcotic intraoperatively was pain associated with surgical manipulations. Postoperatively, instead of using a visual analogue scale for evaluating pain, we chose the need for narcotics to control pain as the basis of comparison because it is more objective and closer to everyday practice. The type of narcotic used was left to the treating physician. Intraoperatively, either morphine or fentanyl was used for supplementary analgesia. The degree of intraoperative analgesia was arbitrarily rated "excellent" if no supplementation was required; "very good" if the narcotic required was 5 mg (or less) morphine or its equivalent of fentanyl based on the assumption that 100  $\mu\text{g}$  fentanyl being equal to 8 mg morphine (11); "good" if the amount of narcotic needed was between 5.1 and 10 mg morphine (or its equivalent); and "poor" if the amount of narcotic required exceeded 10 mg morphine (or its equivalent), or if general anesthesia was needed.

Postoperative analgesia was evaluated by determining the time between subarachnoid injection and the need for analgesia as well as the total dose of narcotic required in 24 hours. Parenteral morphine was used when additional postoperative analgesia was needed during the first 24 hours after surgery. After that, oral Vicodin tablets were given; each tablet contains 5 mg hydrocodone bitartrate (an opioid analgesic) and 500 mg acetaminophen (a nonopioid nonsteroidal analgesic).

The times of bupivacaine injection, start of surgery, delivery, and termination of surgery were recorded. The time of onset and the level of spinal anesthesia, as well as the degree of motor paralysis were determined 2, 5, 10, 15, and 20 minutes after the spinal injection. The times to two-segment regression

Table 1. Times

	Study group (n = 17)	Control group (n = 17)
Induction to delivery (min)	11 ± 1*	13 ± 2
Duration of surgery (min)	54 ± 3	62 ± 5
Recovery room stay (min)	111 ± 8	107 ± 10
Induction to first ambulation (hr)	23.6 ± 2.6	22.1 ± 2.8
Hospital stay (days)	4.5 ± 0.3	4.8 ± 0.6

\*Mean ± SEM. There was no statistical difference.

Table 2. Neonatal condition

	Study group (n = 17)	Control group (n = 17)
Neonatal weight (G)	3021 ± 310*	3371 ± 109
Apgar score		
1 min (range)	7-9	7-9
5 min (range)	8-10	8-10
U.V.		
pH	7.31 ± 0.01	7.32 ± 0.01
Pco <sub>2</sub>	47.2 ± 2.2	44.9 ± 1.2
Po <sub>2</sub>	28.4 ± 0.3	31.6 ± 1.4
BE	-1.9 ± 0.4	-2.1 ± 0.5
U.A.		
pH	7.22 ± 0.01	7.26 ± 0.01
Pco <sub>2</sub>	59.6 ± 2.0	58.1 ± 2.1
Po <sub>2</sub>	20.3 ± 1.5	21.4 ± 1.8
BE	-2.9 ± 0.5	-3.4 ± 1.1

\*Mean ± SEM. There was no statistical difference between the study and control groups.

and complete sensory and motor recovery were also recorded.

The neonatal condition was evaluated using 1- and 5-minute Apgar scores and arterial and venous umbilical blood gas tensions and acid-base status.

For statistical analysis, numerical variables (e.g., age, weight, and dermatomal level of anesthesia) were compared using a two-sample Student's *t*-test. When using a categorical variable (e.g., degree of analgesia) a  $\chi^2$ -test was performed; *P* < 0.05 was considered statistically significant. Data are expressed as mean ± SEM.

## Results

There was no statistical difference between the two groups in age, weight, height, gravidity, parity, or gestational age. The doses of bupivacaine in the study and control groups were comparable: 9.3 ± 0.2 and 9.2 ± 0.2 mg, respectively. Levels of the sensory anesthesia and motor blockade, time to two-segment regression, and time to complete motor or sensory recovery were also similar in both groups. The time

Table 3. Narcotic Requirements\*

	Study group (n = 17)	Control group (n = 17)	P Value
Morphine (mg)			
Intraoperative	1.0 ± 0.6†	7.4 ± 1.7	0.001
In first 24 hr	7.2 ± 3.9	26.8 ± 5.6	0.008
Lumbar puncture to first postoperative need for narcotic (hr)	27.0 ± 7.3	2.0 ± 0.3	0.01

\*Morphine or morphine equivalents (see text).

†Mean ± SEM.

Table 4. Intraoperative Analgesia Score\*

	Study group n = 17 (%)	Control group n = 17 (%)
Excellent	14 (82)	7 (41)
Very good	1 (6)	0 (0)
Good	2 (12)	9 (53)
Poor	0 (0)	1 (6)

\*Significant differences between the two groups, *P* < 0.01.

Table 5. Number of Patients and Narcotic Requirement

	Study group n = 17 (%)	Control group n = 17 (%)
Narcotics required		
Intraoperative	3 (18)	10 (59)*
In 24 hr	6 (35)	17 (100)*

\*Significant differences between the two groups, *P* < 0.01.

between induction and delivery, duration of surgery, duration of stay in the recovery room, time to first ambulation and duration of hospitalization were similar in both groups (Table 1). The neonatal condition was also similar and none of the neonates had an Apgar score of less than 7 or required resuscitation (Table 2).

The intraoperative and postoperative narcotic requirement during the first 24 hours was significantly less in the study group (Table 3). The intraoperative analgesia score in the study group was significantly better, i.e., 88% had "excellent" or "very good" analgesia, compared with 41% in the control group (Table 4). Significantly fewer patients in the study group required intra- and postoperative analgesics (Table 5). The time until postoperative narcotics was needed averaged 27 ± 7.3 and 2 ± 0.3 hours in the study and control groups, respectively, i.e., significantly prolonged with the use of intrathecal morphine (*P* < 0.01).

Vomiting was more frequent intraoperatively in the control patients. Postoperatively, the incidence of nausea and pruritus was higher in the study group (Table 6). Respiratory rates were similar in both

Table 6. Side Effects

	Study group <i>n</i> = 17 (%)	Control group <i>n</i> = 17 (%)
Intraoperative		
Hypotension	14 (82)	12 (71)
Nausea	8 (47)	10 (59)
Vomiting	1 (6)	5 (29)*
Pruritus	0 (0)	0 (0)
Postoperative		
Nausea	5 (29)	1 (6)*
Vomiting	2 (12)	2 (12)
Pruritus	11 (65)	3 (18)*

\*Significant difference,  $P < 0.05$ .

Table 7. Frequency and Duration of Decreases in Oxygen Saturation

Sao <sub>2</sub> (%)	Study group ( <i>n</i> = 6)		Control group ( <i>n</i> = 11)	
	<i>n</i> (%)	Total duration (min)	<i>n</i> (%)	Total duration (min)
90-85	1 (17)	3	10 (91)	203*
85-80	1 (17)	1	5 (46)	32*

\*Significant differences between the two groups,  $P < 0.05$ .

groups, none being below 10 breaths/min. The pulse oximeter was applied for an average of 22 hours (range 20 to 29). The oxygen saturation values, as recorded on an hourly basis, were similar in both the study and control groups:  $95.5 \pm 0.3$  and  $95.6 \pm 0.8\%$ , respectively. However, close examination of the histograms showed significantly more frequent and more prolonged depression of Sao<sub>2</sub>% in more patients in the control group than in the study group (Table 7).

Intravenous naloxone was used in two patients in the study group, the doses being 0.2 mg to treat pruritus, and 0.3 mg for nausea and vomiting. The postoperative cardiovascular status, as evaluated by the heart rate and arterial blood pressure, was similar in both groups. None of the patients complained of postspinal headache.

## Discussion

The addition of 0.2 mg morphine to spinal hyperbaric bupivacaine affected neither the levels of sensory or motor blockade nor the rates at which they regressed. However, this simple technique significantly improved intraoperative and postoperative analgesia. It has been reported that epidural and intrathecal opiate analgesia in high-risk patients are associated with early postoperative ambulation and shorter hospital stay (12). In our study, neither the time to ambulation

nor the duration of hospitalization was shorter in patients given intrathecal morphine. This difference between our findings and those reported by others (12) might have been due to the fact that our patients were young and healthy, with a lower abdominal operation and a rewarding outcome of the operative procedure. Because pain can cause tachycardia and hypertension, we were expecting a significant difference in the postoperative cardiovascular status between the two groups. However, the absence of such a difference was probably due to the close attention paid to pain relief in all patients. It is known that hypotension is an important cause of vomiting (13). The decreased incidence of intraoperative vomiting in the study group, despite the equal incidence of hypotension in both groups, might have been due to decreased use of parenteral narcotics. The effect of morphine on urinary retention was irrelevant in our study because of the routine use of an indwelling urinary catheter in all patients.

For evaluating the effect on the fetus and neonate, we used the Apgar scores, the umbilical acid-base status, and blood gas tensions. The absence of any significant effect of intrathecal morphine on the fetus or neonate confirms previous studies in which larger doses of intrathecal morphine were used (4,5,14).

In our study, no evidence of respiratory depression was found after intrathecal morphine. This is in contrast to data from two nationwide Swedish surveys (8,15). The more favorable results in our study may be due to the limited number of patients, but other factors may include the smaller dosage of intrathecal morphine in our study, the absence of premedication, the healthy condition and young age of our patients, and the stimulation of the respiratory centers during pregnancy (16). Since completion of this study, we routinely use this technique for cesarean section, monitoring the respiration by pulse oximetry and collecting data to evaluate its safety. So far, 56 additional patients have been studied without respiratory depression and with excellent intra- and postoperative analgesia.

The depression of Sao<sub>2</sub>% with postoperative parenteral administration of narcotics was unexpected. A possible explanation for this may be that parenteral narcotics caused fluctuations in CNS status with periods of excessive depression reflected in decreased Sao<sub>2</sub>%. Our finding of respiratory depression after parenteral morphine has been confirmed by two other investigators (17,18). Respiratory depression after parenteral narcotic administration may be more frequent than is commonly believed. With the use of 0.2 mg intrathecal morphine, however, subsequent use of narcotics did not lead to respiratory depression



and thus patients given intrathecal morphine in the small doses we used need not be deprived of postoperative narcotic administration when indicated.

By using small doses of naloxone, side effects such as pruritus and vomiting were managed without reversing the analgesia.

Rawal (19) found the use of intraspinal morphine to be associated with fewer postlumbar puncture headaches. However, the number of cases in our study is too small to make any meaningful comparison.

We conclude that the addition of 0.2 mg morphine to hyperbaric spinal bupivacaine is a simple, safe means of improving intraoperative analgesia and providing prolonged postoperative analgesia and, also, that parenteral administration of narcotics appears to be more depressant to respiration than is commonly believed.

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## Cimetidine Does Not Inhibit Plasma Cholinesterase Activity

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COOK DR, STILLER RL, CHAKRAVORTI S, MANNENHIRA T. Cimetidine does not inhibit plasma cholinesterase activity. *Anesth Analg* 1988;67:375-6.

*Cimetidine increases the duration of action of succinylcholine several-fold by an unknown mechanism. The hydrolysis rate of succinylcholine by human plasma was measured with a modified spectrophotometric assay. At a*

*concentration of 1-50 µg/ml cimetidine did not inhibit the hydrolysis of succinylcholine. It is concluded that cimetidine may have an effect at the neuromuscular junction but does not inhibit plasma cholinesterase.*

Key Words: NEUROMUSCULAR RELAXANTS—succinylcholine. PHARMACOLOGY—cimetidine.

Acute administration of cimetidine, an H<sub>2</sub>-receptor antagonist, increases the duration of action of succinylcholine several-fold (1). Although cimetidine is associated with a direct inhibition of liver microsomal enzymes and a decrease in liver blood flow (2,3), the mechanism for the prolongation of the neuromuscular blockade from succinylcholine is unclear. We speculated that cimetidine was a pseudocholinesterase inhibitor. We therefore investigated the effects of cimetidine at clinically relevant concentrations on pseudocholinesterase activity by using succinylcholine as a substrate.

### Methods

Cimetidine (1, 2, 5, 10, 20, 50, and 200 µg/ml plasma) was incubated (in duplicate) with 50 µl human plasma of known (plasma) butyrylcholinesterase activity (EC 3.1.1.8) in buffer (pH 7.4) for 20 minutes. Succinylcholine (0.5 µmol) was added and the mixture incubated for another 20 minutes. The reaction was stopped with ethothiophate iodide. The hydrolysis of succinylcholine was measured by a modified spectrophotometric assay (4,5). The hydrolysis reaction of succinylcholine by butyrylcholinesterase was coupled with choline oxidase and peroxidase in the presence of 4-aminoantipyrine and phenol to produce a red quinone dye. The absorption of the quinone dye produced was measured at 500 nM with

a Beckman spectrophotometer. Appropriate blanks were used to correct for the spontaneous hydrolysis of succinylcholine. Standard curves relating choline concentration and absorbance were constructed using choline chloride.

The enzyme activity for succinylcholine at each concentration of cimetidine was expressed as micromoles hydrolyzed per minute per liter plasma at 37°C ( $\mu\text{mol}\cdot\text{min}^{-1}\cdot\text{L}^{-1}$  or units per liter [U/L]).

### Results

The human plasma had a pseudocholinesterase activity of 2900 U/L ( $\mu\text{mol}$  acetylthiocholine iodide hydrolyzed per minute per liter plasma at 37°C). In the absence of cimetidine, human plasma hydrolyzed succinylcholine at a rate of 118 U/L. The standard deviation was 2.5 U/L with a coefficient of variation of 5%. Cimetidine at concentrations of 1-50 µg/ml did not inhibit the hydrolysis of succinylcholine. Cimetidine at 200 µg/ml inhibited the hydrolysis of succinylcholine by 15% (Table 1).

### Discussion

Cimetidine is frequently used on either an acute or a chronic basis to control the pH and volume of gastric contents. Following oral administration of the usual dose (300 mg) the peak plasma concentrations range from 1-10 µg/ml (6,7). At clinically relevant concentrations cimetidine does not inhibit the in vitro hydrolysis of succinylcholine by plasma cholinesterase.

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Table 1. Summary of Data

Cimetidine concentration ( $\mu\text{g/ml}$ plasma)	Succinylcholine hydrolysis rate* (U/L)
0	118
1	126
2	114
5	123
10	118
20	121
50	115
200	101

\*Mean value.

Although cimetidine influences the pharmacokinetics of a variety of drugs (8-10), it is difficult to envision that inhibition of microsomal enzymes or a decrease in liver blood flow would influence the pharmacodynamics of succinylcholine. Therefore, one suspects that the interaction of cimetidine and succinylcholine is at the neuromuscular junction. One wonders if such interactions occur with other relaxants because cimetidine is used along with  $H_1$ -receptor antagonists to attenuate histamine-related side effects from relaxants (11). This possibility needs to be investigated further.

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# Sedative Doses of Midazolam Depress Hypoxic Ventilatory Responses in Humans

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ALEXANDER CM, GROSS JB. Sedative doses of midazolam depress hypoxic ventilatory responses in humans. *Anesth Analg* 1988;67:377-82.

*The effect of midazolam on the hypoxic ventilatory response of eight healthy volunteers was examined during isocapnic rebreathing. The magnitude of the slope of the ventilatory response to hypoxia ( $\dot{V}_E$  vs  $\text{SaO}_2$ ) decreased from  $1.48 \pm 0.24$  to  $0.70 \pm 0.13 \text{ L}\cdot\text{min}^{-1}\cdot\%\text{SaO}_2^{-1}$  ( $\bar{x} \pm \text{SE}$ ,  $P < 0.005$ ) after midazolam  $0.1 \text{ mg/kg}$  IV. The calculated ventilation at an arterial saturation of 90% also decreased from  $28.6 \pm 4.4$  to  $19.9 \pm 2.7 \text{ L/min}$  ( $P < 0.05$ ). Before midazolam, hypoxia to an  $\text{SaO}_2$  of  $75 \pm 2\%$  was associated with a  $23 \pm 3$  beats/min increase in heart rate; after midazolam, the increase in heart rate with hypoxia was only  $4 \pm 2$  beats/min ( $P < 0.001$ ). Additionally, a double-blind crossover study evaluated the effect of physostigmine on awareness and hypoxic ventilatory response*

*after midazolam. The change in hypoxic response slope after physostigmine  $2.0 \text{ mg}$  IV (an increase of  $0.28 \pm 0.34 \text{ L}\cdot\text{min}^{-1}\cdot\%\text{SaO}_2^{-1}$ ) did not differ significantly from that after placebo (an increase of  $0.03 \pm 0.22 \text{ L}\cdot\text{min}^{-1}\cdot\%\text{SaO}_2^{-1}$ ), although physostigmine significantly increased awareness. It is concluded that a sedative dose of midazolam depresses hypoxic ventilatory response and attenuates the hyperpnea and tachycardia associated with hypoxemia. Furthermore, physostigmine-glycopyrrolate reversal of midazolam-induced sedation was associated with nausea (five subjects), vomiting (three subjects), and tachycardia without reversal of the depressed hypoxic ventilatory response.*

**Key Words:** ANTAGONISTS, MISCELLANEOUS—physostigmine. ANTAGONISTS, CHOLINERGIC—glycopyrrolate. HYPNOTICS, BENZODIAZEPINES—midazolam. VENTILATION—hypoxic response.

Midazolam is a water-soluble benzodiazepine frequently used for "conscious sedation" during procedures such as bronchoscopy, cystoscopy, or gastrointestinal endoscopy (1), as well as during regional anesthesia. Previous studies show that hypnotic doses of midazolam (2) and diazepam (3) decrease ventilation and/or the slope of the CO response curve; for sedative doses, the results have been more variable (4). Small concentrations (0.1 MAC) of general anesthetics such as halothane virtually eliminate hypoxic drive, although they have little effect on the ventilatory response to hypercarbia (5), suggesting

that the former may be more sensitive to pharmacologic suppression. Therefore, we designed this study to examine the effect of a sedative dose of midazolam (0.1 mg/kg) on hypoxic ventilatory response. Additionally, because of a previous clinical report showing that physostigmine reverses midazolam sedation (6), we investigated the effects of physostigmine on ventilatory drive and level of consciousness after the administration of midazolam.

## Methods

After approval by our institutional review board, we obtained written informed consent from nine healthy volunteers weighing 61 to 87 kg and ranging in age from 25 to 37 years; eight subjects completed the protocol (vide infra). Subjects abstained from beverages containing alcohol and caffeine for 24 hours and had nothing by mouth for at least 8 hours before the start of the study; all had normal hematocrits and negative urinalyses for protein and glucose, were nonsmokers, and had not used benzodiazepines for

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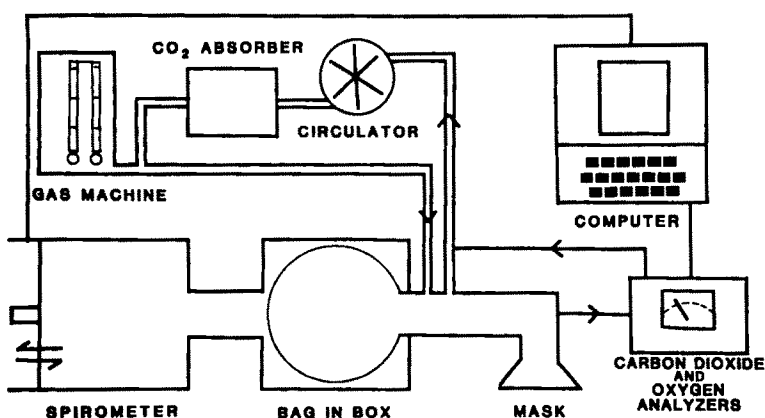


Figure 1. Breathing circuit for maintaining isocapnic conditions during progressive hypoxia. By adjusting the speed of the circulator, we could control the amount of  $\text{CO}_2$  in the circuit, enabling us to maintain end-tidal  $\text{CO}_2$  constant to within 1 mm Hg.

at least 14 days. Before each study, we started an infusion of normal saline (100 ml/hr), applied blood pressure (oscillotonometer) and ECG monitors, and recorded baseline measurements. An Ohmeda 3700 pulse oximeter (Version J), operating in the fast (3-second averaging) mode, continuously measured arterial oxygen saturation via an ear probe.

The supine subjects listened to symphonic music through headphones as they breathed mixtures of  $\text{O}_2$  in  $\text{N}_2$  at constant  $\text{CO}_2$  tensions through the circuit shown in Figure 1. Instrumentation Laboratory End-tidIL 200 infrared  $\text{CO}_2$  analyzer, calibrated using standard gas mixtures, continuously measured airway  $\text{CO}_2$  tension. By varying the speed of the circulator in the breathing circuit, we adjusted flow through the  $\text{CO}_2$  absorber to keep end-tidal  $\text{CO}_2$  tensions constant ( $\pm 1$  mm Hg). At a flow of 100 L/min, resistance to gas flow in the circuit was 0.02 cm  $\text{H}_2\text{O} \cdot \text{L}^{-1} \cdot \text{min}$ . An Electro/Med 780 rolling seal spirometer (previously calibrated with a 2-L calibrating syringe) measured tidal volume. A Yellow Springs Instruments 400 series thermistor measured the temperature of the bag in the box; we converted all volumes to BTPS using standard formulas. The  $\text{CO}_2$  analyzer, spirometer, and pulse oximeter were interfaced to a CBM 8032 computer by a multichannel analog-to-digital converter.

We determined baseline values for the ventilatory response to hypoxia using the isocapnic rebreathing method (7). After filling the circuit with 21%  $\text{O}_2$  in  $\text{N}_2$ , we allowed subjects to equilibrate to an end-tidal  $\text{Pco}_2$  of approximately 50 mm Hg for 8 min. We chose this  $\text{CO}_2$  tension, because it is slightly above what we expected to observe after midazolam administration. This allowed us to perform all of our study phases at the same  $\text{PET}_{\text{CO}_2}$ , thus assuring a constant hypercarbic stimulus to ventilation. We supplied sufficient oxygen to maintain the volume of gas in the circuit and an  $\text{FI}_{\text{O}_2}$  of approximately 0.21. At the end of this equilibration period, we terminated oxy-

Table 1. Definition of Awareness Scores

4	Awake and alert
3	Awake but drowsy
2	Asleep but arousable
1	Asleep and unarousable, lash reflex present
0	Asleep, lash reflex absent

gen flow into the circuit and substituted an equal flow of nitrogen, allowing the volume of gas in the spirometer to remain constant. Rebreathing then progressively lowered inspired oxygen concentrations. When the arterial  $\text{O}_2$  saturation reached 85%, we added 1 ml  $\cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  oxygen to the circuit to slow the decrease in  $\text{FI}_{\text{O}_2}$ . We discontinued each run when  $\text{SaO}_2$  reached 75%. However, if a subject became agitated, we immediately discontinued the study; in all cases,  $\text{SaO}_2$  reached 80% before this occurred. Before and after each hypoxic drive determination, we recorded blood pressure, heart rate and level of consciousness (five-point scale, Table 1).

While the subjects breathed room air, we then administered midazolam 0.1 mg/kg IV over 5 minutes. After an 8-minute equilibration at the same end-tidal  $\text{CO}_2$  tension used above, we repeated the hypoxic ventilatory response measurement.

We used a randomized, double-blind crossover design (8) to determine the effect of physostigmine on hypoxic ventilatory response and level of consciousness: After the post-midazolam hypoxic drive determination, subjects received their first "reversal" injection IV (physostigmine 2 mg plus glycopyrrolate 0.2 mg or an equal volume of saline) injected over 5 minutes. Syringes were prepared by an individual not otherwise involved in the study; their contents were unknown to both the investigators and subjects until the studies were completed. We allowed 5 minutes for the treatment to take effect and then determined "post-treatment #1" hypoxic drive determination at the same end-tidal  $\text{CO}_2$  tension used

previously. When this was complete, subjects received their second "reversal" injection (saline or physostigmine-glycopyrrolate, whichever was not contained in the first syringe). After allowing 5 minutes for this injection to take effect, we determined the "post-treatment #2" ventilatory drive. Subjects then returned to the recovery room for observation until they were fully awake.

## Data Analysis

For each five breaths we computed mean minute ventilation and arterial saturation. Using linear regression, we calculated the slope of  $\dot{V}_E$  vs arterial saturation in the range of 95–75% to quantitate the ventilatory response to hypoxia during each hypoxic response measurement (i.e., before midazolam, after midazolam, and after each "reversal" syringe). Because ventilation increases as arterial saturation decreases, these slopes have negative signs. To allow larger values to indicate greater hypoxic drive, we will refer to the absolute values of the slopes in the remainder of the discussion. We compared changes in displacement of the  $\dot{V}_E$  vs  $\text{SaO}_2$  line by calculating  $\dot{V}_{90}$ , the minute ventilation at an arterial saturation of 90%. We also computed the mean end-tidal  $\text{CO}_2$  tension for each hypoxic study to document that there was no variation between study phases.

Two-way analysis of variance assessed the effect of midazolam on hypoxic drive slope,  $\dot{V}_{90}$ , resting heart rate, and resting blood pressure. We analyzed the effect of midazolam on hypoxia-induced changes in heart rate and blood pressure in the same manner. By subtracting each subject's post-midazolam slope from his or her post-treatment #1 slope, we calculated the change in slope associated with the first reversal injection. Similarly, by subtracting the post-treatment #1 slope from the post-treatment #2 slope, we determined the change in slope associated with the second reversal injection. To compare the changes in hypoxic drive slope associated with physostigmine to those associated with saline placebo, we used two-factor analysis of variance for four replications (9). This model allowed us to determine if changes in slope were related to the contents of the "reversal" syringes or to waning of the ventilatory depressant effect of midazolam with time. We used the same two-way analysis of variance model to analyze the changes in awareness, heart rate, blood pressure, and  $\dot{V}_{90}$  after each "reversal" injection. For all analyses,  $P < 0.05$  indicated statistical significance.

**Table 2.** Mean  $\text{CO}_2$  Tensions and Minimum  $\text{SaO}_2$  Achieved during Each Study Phase ( $\bar{x} \pm \text{SE}$ )

Study phase	End-tidal $\text{CO}_2$ tension (mm Hg)	Minimum $\text{SaO}_2$ (%)
Before midazolam	$50.0 \pm 0.7$	$75.1 \pm 1.6$
After midazolam	$50.0 \pm 0.8$	$77.0 \pm 1.1$
Post-treatment #1	$50.2 \pm 0.9$	$77.6 \pm 1.5$
Post-treatment #2	$50.0 \pm 0.9$	$76.5 \pm 1.2$

## Results

None of our subjects reported unpleasant sensations during midazolam injection. Although they did not lose consciousness or develop airway obstruction, in two subjects oxygen saturations dropped below 90% (while breathing room air) after midazolam administration. Their oxygenation improved and stabilized above 90% when we encouraged them to take deep breaths of air. After physostigmine administration, five subjects became nauseated. Three of them vomited. We were unable to obtain usable data from one subject who became agitated whenever  $\text{SaO}_2$  was less than 85% after midazolam. End-tidal  $\text{CO}_2$  tensions were stable to within  $\pm 1$  mm Hg during each hypoxic ventilatory determination; they did not vary significantly among the four study phases (Table 2). The mean minimum arterial saturation achieved during hypoxia was  $76 \pm 1\%$  ( $\bar{x} \pm \text{SEM}$ ); there was no significant difference among the four study phases.

Slopes (absolute values v.s.) of the hypoxic ventilatory response ( $\dot{V}_E\text{RO}_2$ ), ventilation at an arterial saturation of 90% ( $\dot{V}_{90}$ ), and awareness scores during each rebreathing determination appear in Table 3. The first four rows contain data for those subjects who received saline as their first reversal; the second four rows contain data from subjects who received physostigmine as their first reversal.

After injection of midazolam 0.1 mg/kg, the slope of  $\dot{V}_E\text{RO}_2$  decreased significantly from  $1.48 \pm 0.24$  to  $0.70 \pm 0.13 \text{ L}\cdot\text{min}^{-1}\cdot\%\text{SaO}_2^{-1}$  ( $\bar{x} \pm \text{SE}$ ). The  $\dot{V}_{90}$  also decreased from  $28.57 \pm 4.41$  to  $19.9 \pm 2.72 \text{ L/min}$ . We completed the tests of subjects' hypoxic ventilatory responses 16  $\pm$  3 minutes after completion of midazolam administration.

The change in hypoxic drive slope after physostigmine (an increase of  $0.28 \pm 0.34 \text{ L}\cdot\text{min}^{-1}\cdot\%\text{SaO}_2^{-1}$ ) did not differ significantly from that after placebo (an increase of  $0.03 \pm 0.22 \text{ L}\cdot\text{min}^{-1}\cdot\%\text{SaO}_2^{-1}$ ); similarly, the change in  $\dot{V}_{90}$  after physostigmine (an increase of  $4.44 \pm 2.42 \text{ L/min}$ ) was not different from the change after placebo (an increase of  $2.50 \pm 3.53 \text{ L/min}$ ). The change in slope of all subjects'  $\dot{V}_E\text{RO}_2$  after their first reversal injection (regardless of its contents) was  $+0.61 \pm 0.24 \text{ L}\cdot\text{min}^{-1}\cdot\%\text{SaO}_2^{-1}$ . This

Table 3. Ventilation and Awareness after Midazolam and Physostigmine\*

All subjects						Subjects receiving		
Before midazolam			After midazolam			Placebo (NaCl)		
Slope	$\dot{V}_{90}$	Awareness	Slope	$\dot{V}_{90}$	Awareness	Slope	$\dot{V}_{90}$	Awareness
1.83	26.8	4.0	0.55	17.0	2.0	0.89	21.1	3.0
2.39	48.2	4.0	1.46	27.3	2.0	2.50	48.3	2.5
1.02	28.1	4.0	0.75	32.2	3.0	0.79	31.2	3.0
0.83	27.7	4.0	0.31	15.8	1.0	0.65	25.9	2.0
2.11	44.9	4.0	0.93	26.1	2.5	—	—	—
1.10	23.3	4.0	0.46	17.0	2.0	—	—	—
0.54	14.5	4.0	0.36	9.8	1.0	—	—	—
2.03	14.2	4.0	0.80	14.0	2.0	—	—	—
Mean 1.48	28.5	4.0	0.70†	19.9‡	1.9†	1.21	31.6	2.6
SEM 0.24	4.4	0	0.13	2.7	0.2	0.43	5.9	0.2

\*Values represent slopes of the hypoxic response ( $L \cdot \min^{-1} \cdot \%SaO_2^{-1}$ ) multiplied by  $-1$  (see text), computed ventilation at  $SaO_2 = 90\%$ , and mean awareness scores (Table 1) averaged during each hypoxic response determination. The first four rows present data from subjects who received saline as their first reversal; the last four present data from subjects who received physostigmine first.

† $P < 0.005$  compared with premidazolam value.

‡ $P < 0.05$  compared with premidazolam value.

was significantly greater than the change observed after the second reversal injection ( $-0.30 \pm 0.22 L \cdot \min^{-1} \cdot \%SaO_2^{-1}$ ). Therefore, injection sequence rather than injection content was more important in determining the ventilatory effect of our reversal treatments.

After saline injection, awareness scores decreased by  $0.1 \pm 0.2$ ; after physostigmine, awareness scores increased by  $1.0 \pm 0.2$ . The increase associated with physostigmine was significantly greater than that associated with saline. Changes in awareness associated with the first ( $0.8 \pm 0.3$ ) and second ( $0.1 \pm 0.3$ ) reversal injections were also significantly different. Therefore, both syringe content and the effect of time were important in determining the effect of reversals on our subjects' level of consciousness.

Before midazolam, hypoxia caused subjects' heart rates to increase by  $23 \pm 3$  beats/min; after midazolam this increase was only  $4 \pm 2$  beats/min. Hypoxia did not affect blood pressure before or after midazolam administration. The physostigmine-glycopyrrolate mixture was associated with a significant increase in our subjects' heart rates ( $26 \pm 8$  beats/min), compared with saline placebo ( $8 \pm 8$  beats/min).

## Discussion

Hypoxic drive can be quantitated in several ways. One way is to use the shape factor "A" that describes the curvature of hyperbolic relation between  $\dot{V}_E$  and  $Pao_2$  (10); however, the value of A depends on the arbitrarily chosen vertical asymptote (usually assumed to be 32–40 mm Hg). Alternatively, the relationship  $\dot{V}_E$  vs arterial saturation (measured by ear

oximeter) is linear with its slope indicating the magnitude of hypoxic drive (7). Our plots of minute ventilation in response to decreases in arterial saturation were linear with correlation coefficients  $>0.8$  and slopes within the range previously reported. The Ohmeda 3700 oximeter, equipped with ear probe, accurately estimates arterial saturation under conditions similar to those of the present study (11).

We found that midazolam, 0.1 mg/kg (at the low end of the 0.1 to 0.15 mg/kg recommended dose range for sedation during invasive procedures [12]) significantly decreases hypoxic ventilatory response in hypercarbic volunteers. After midazolam, the slope (absolute value, v.s.) of the line relating  $\dot{V}_E$  to  $SaO_2$  decreased by 53%. This result is strikingly similar to that reported by Lakshminarayan et al. (13), who found a 53% decrease in hypoxic drive when volunteers were given diazepam 10 mg IM.

Because doses of midazolam similar to those used in the present study do not affect the ventilatory response to  $CO_2$  (14), we initially assumed that clinically significant respiratory depression would not occur with midazolam as used in the present study (15). However, two of our subjects became hypoxic shortly after midazolam; this could have resulted from an acute decrease in hypercarbic drive associated with their decreased level of consciousness. The resulting hypoventilation could have caused a rapid decrease in alveolar and arterial  $O_2$  tensions until hypercarbia or external arousal were sufficient to stimulate ventilation. In unmedicated individuals, hypoxic drive provides protection from hypoventilation-induced hypoxia. However, we have shown that midazolam ablates this protective mechanism in these circumstances (hypoxemia superimposed on



Table 3 (continued)

placebo first			Subjects Receiving physostigmine first					
Physostigmine			Physostigmine			Placebo (NaCl)		
Slope	$\dot{V}_{90}$	Awareness	Slope	$\dot{V}_{90}$	Awareness	Slope	$\dot{V}_{90}$	Awareness
1.23	22.1	3.0	—	—	—	—	—	—
1.42	39.2	3.5	—	—	—	—	—	—
1.36	44.2	4.0	—	—	—	—	—	—
-0.04	35.1	3.0	—	—	—	—	—	—
—	—	—	1.70	26.8	3.0	1.25	21.7	2.0
—	—	—	0.42	22.2	3.0	0.66	19.7	3.0
—	—	—	0.71	18.6	3.0	0.37	14.6	2.0
—	—	—	2.84	20.7	3.0	1.86	18.0	3.0
0.99	35.1	3.4	1.42	22.1	3.0	1.03	18.5	2.5
0.35	4.7	0.2	0.55	1.7	0	0.33	1.5	0.3

hypercarbia). Therefore, even patients with normal lungs and respiratory function may be at risk for the development of hypoxia after midazolam. This risk may be significantly increased in patients with  $\text{CO}_2$  retention, who are chronically dependent on hypoxic drive, as well as in patients recovering from inhalation or IV anesthetics that may further depress ventilation.

Our data also suggest that sedation with midazolam may make detection of hypoxemia more difficult because some of the clinical signs of hypoxemia may be decreased or absent. The attenuation of the hypoxic ventilatory response by midazolam means that hypoventilation may occur during hypoxemia. Additionally, after midazolam, hypoxia is not associated with tachycardia. Thus, hypoxemia may be associated only with cyanosis and changes in mental status. The latter may easily be confused with the need for further sedation; indeed, one of our subjects became confused during hypoxia in the post-midazolam phase. The detection of cyanosis is unreliable in the presence of anemia, pigmented skin, or poor lighting. In addition, procedures such as cystoscopy or endoscopy typically require the physician to use equipment that may obscure his or her view of the patient. Our results suggest that continuous monitoring of  $\text{O}_2$  saturation should be considered for patients who are sedated with midazolam.

Two-way analysis of variance enabled us to differentiate the effects of reversal syringe content from the waning effect of midazolam with time. Physostigmine had no significant effect on midazolam-induced depression of the hypoxic ventilatory response. The first reversal injection, regardless of syringe content, was significantly associated with an improvement in both hypoxic response and awareness scores, suggesting that the midazolam effect was waning more rapidly at the time of the first reversal than at the time of the second. The short half-life of midazolam may

have limited our ability to demonstrate a significant effect of physostigmine; we previously showed that the effect of midazolam on hypercarbic ventilatory drive lasts only about 15 minutes (2). Furthermore, our findings were consistent with data showing that after diazepam 0.4 mg/kg, physostigmine actually decreased the ventilatory response to hypercarbia (8).

In contrast to our findings on the effects of physostigmine on ventilatory responses to hypoxia following midazolam, awareness scores increased more after physostigmine injection than after placebo. This is consistent with earlier reports of physostigmine reversal of benzodiazepine-induced sedation (6,8,16); it also provides evidence of a persistent CNS effect of midazolam at the time of physostigmine administration (v.s.). It is important to note that although patients may "wake up" after physostigmine, their ability to respond to hypoxic stress is still compromised. The increased level of consciousness could lull those caring for the patient into a false sense of security.

Physostigmine is not a benign drug; it causes peripheral cholinergic side effects including bradycardia, nausea, vomiting, and salivation. Five of our subjects developed nausea or vomiting after physostigmine, suggesting that glycopyrrolate 0.2 mg is insufficient to block gastrointestinal side effects in adult patients. Because it has a quaternary nitrogen, glycopyrrolate it does not cross the blood-brain barrier; therefore it should not have affected our measurements of consciousness or ventilation. However, glycopyrrolate did increase the heart rate significantly. Because physostigmine-glycopyrrolate reversal of benzodiazepine-induced sedation is associated with significant side effects and no improvement of hypoxic ventilatory response, this combination should be used with caution for treatment of midazolam-induced respiratory depression.

In conclusion, midazolam decreases hypoxic ven-

tilatory response and may make detection of hypoxemia more difficult. This is especially significant in patients chronically dependent on hypoxic drive, those who have surgical or medical problems which predispose them to hypoxia, and those given anesthetics or other drugs that may depress ventilation. Sedation with midazolam should be accompanied by continuous monitoring of arterial oxygen saturation.

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## Regional Cerebral Blood Flow and Response to Carbon Dioxide during Controlled Hypotension with Isoflurane Anesthesia in the Rat

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RINGAERT KRA, MUTCH WAC, MALO LA. Regional cerebral blood flow and response to carbon dioxide during controlled hypotension with isoflurane anesthesia in the rat. *Anesth Analg* 1988;67:383-8.

Regional (frontal, parietal, occipital, cortical, and basal ganglia) cerebral blood flow (rCBF) was examined at 1.5 and 3.5 MAC inspired isoflurane/O<sub>2</sub> anesthesia in the rat using the radioactive microsphere technique to determine the effects of controlled hypotension with deep isoflurane anesthesia on rCBF and the response of rCBF to changes in Paco<sub>2</sub> when mean blood pressure (BP) was decreased to levels below the lower limit of the autoregulatory threshold. Four groups of six rats were studied with rCBF 1 determined at 1.5 MAC (mean BP 80-90 mm Hg) followed by two rCBF determinations at 3.5 MAC (mean BP 46-48 mm Hg). For CBF 1 the regional CO<sub>2</sub> response was a 3.1-3.9% increase in rCBF/mm Hg increase in CO<sub>2</sub>. Regional cerebral blood flow (ml/g/min) ranged from  $0.64 \pm 0.05$ - $0.83 \pm 0.15$  at Paco<sub>2</sub> of 19 mm Hg to  $1.34 \pm 0.11$ - $1.80 \pm 0.33$

at Paco<sub>2</sub> of 41 mm Hg to  $2.61 \pm 0.26$ - $3.72 \pm 0.37$  at Paco<sub>2</sub> of 59 mm Hg (mean  $\pm$  SEM). With controlled hypotension (CBF 2) rCBF was unchanged during normocarbica, increased 100% during hypocarbica,  $P < 0.01$  vs CBF 1 and decreased 30% during hypercarbica,  $P < 0.01$  vs CBF 1. For rCBF 3 measurements, the BP and inspired concentration of isoflurane were kept constant, while Paco<sub>2</sub> was increased in two and decreased in two of the four groups. Within-group comparisons between rCBF 2 and rCBF 3 results demonstrated loss of CO<sub>2</sub> responsiveness of the rat cerebrovasculature in every region during controlled hypotension to below the autoregulatory threshold at 3.5 MAC isoflurane/O<sub>2</sub> anesthesia. These results show that rCBF is well maintained in normal cerebral tissue when mean BP is decreased to below the autoregulatory threshold during controlled hypotension with deep isoflurane anesthesia.

Key Words: ANESTHETICS, VOLATILE—isoﬂurane.  
ANESTHETIC TECHNIQUES—hypotensive.  
BRAIN, BLOOD FLOW—CO<sub>2</sub> response.

Controlled hypotension is frequently accomplished during neurovascular surgery with high inspired concentrations of isoflurane. Reasons for the popularity of deep isoflurane anesthesia include smooth induction of hypotension with maximal cerebral metabolic depression (1-4). Despite this popularity, little information is available on the effects of controlled

hypotension with deep isoflurane anesthesia on cerebral blood flow when blood pressure is decreased to or below the autoregulatory threshold. This is important information because mean blood pressure below the autoregulatory threshold is often requested by the neurosurgeon to facilitate clipping on cerebral aneurysms. The safe lower limit for mean blood pressure that assures adequate cerebral blood flow during deep isoflurane anesthesia is unknown. The use of the EEG to assess adequacy of cerebral perfusion during deep isoflurane anesthesia is precluded because such isoflurane concentrations result in a flat EEG (5,6). It is also unclear if cerebrovascular responsiveness to CO<sub>2</sub> is maintained during controlled hypotension with deep isoflurane anesthesia when mean blood pressure is below the autoregulatory threshold. Using a dog model, Artru (7) demon-

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strated that when mean blood pressure was reduced to 50 mm Hg with deep isoflurane anesthesia, total cerebral blood flow during hypocarbia ( $\text{Paco}_2$ , 20 mm Hg) was significantly lower than that during normocarbia ( $\text{Paco}_2$ , 40 mm Hg). The  $\text{CO}_2$  responsiveness of the cerebral vasculature in these experiments was maintained at 50% of control levels. This finding differs from results obtained in the same laboratory when other agents were used to induce controlled hypotension (8,9). Thus, at the lower limit of the autoregulatory threshold in the dog (10), there is retained but attenuated  $\text{CO}_2$  responsiveness of the cerebral vasculature with deep isoflurane anesthesia. Whether or not the  $\text{CO}_2$  responsiveness persists below the autoregulatory threshold was not examined.

In the present study, using a rat model we measured regional cerebral blood flow (rCBF) during normotension at 1.5 MAC inspired isoflurane/ $\text{O}_2$  anesthesia and during controlled hypotension below the autoregulatory threshold for CBF at 3.5 MAC using the radioactive microsphere technique to measure rCBF. The  $\text{CO}_2$  responsiveness of the regional cerebral vasculature during low, normal, and high  $\text{CO}_2$  levels for the same two MAC levels has also been examined.

## Methods

These experiments were approved by the Animal Care Committee of the University of Manitoba. Anesthesia was induced with ether in male Long-Evans rats that were then intubated and ventilated with a Harvest rodent ventilator with approximately 1.5 MAC (1 MAC = 1.38% isoflurane in the rat [11]) inspired isoflurane in 100%  $\text{O}_2$ . The isoflurane was delivered using a Dräger Halothan-Vapor calibrated with a Puritan-Bennett 222 anesthetic agent monitor. After establishment of assisted ventilation, the rats were given 0.06 mg atropine and 0.3 mg pancuronium. Atropine was given to block the vagal effects associated with manipulation of the carotid sinus during insertion of the right carotid line. Rectal temperatures were maintained at  $37 \pm 1^\circ\text{C}$ . by servo-controlled heat lamp. Catheters (PE-50) were inserted into the tail and femoral arteries for continuous measurement of arterial blood pressure and arterial blood gas sampling and via the right common carotid into the left ventricle (by pressure monitoring), for radioactive microsphere injection. Blood pressure measurements were made using calibrated Gould P23 transducers referenced to the external auditory meatus.

Four groups of six rats were studied with three periods for rCBF determinations in each rat. In each group, the initial period for rCBF measurements (CBF 1) was during normotension (mean blood pressure, 80–90 mm Hg) with 1.5 MAC inspired isoflurane. In all four groups the initial rCBF determinations were done after rats had stabilized at 1.5 MAC isoflurane anesthesia and the chosen  $\text{Paco}_2$  for a minimum of 1 hour. Before each measurement of rCBF,  $\text{Paco}_2$  was measured and again measured immediately after withdrawal of reference organ blood samples (see later). Regional cerebral blood flow values were plotted against  $\text{Paco}_2$  values obtained after measurements of rCBF. For rCBF 2 and 3 measurements, hypotension (mean blood pressure,  $<50$  mm Hg) was induced by increasing the inspired isoflurane concentration to 3.5 MAC. To assess response of rCBF to changes in  $\text{CO}_2$  in each group, the  $\text{Paco}_2$  was changed before rCBF 3 by altering the dead space of the breathing circuit to produce low (LC), normal (NC), or high (HC)  $\text{Paco}_2$  levels in the following manner: group 1 (NC NC LC), group 2 (LC LC NC), group 3 (NC NC HC), and group 4 (HC HC NC).

Regional cerebral blood flow was determined by left ventricular injection of 500,000 microspheres of 15  $\mu\text{m}$  diameter of either  $^{51}\text{Cr}$ ,  $^{85}\text{Sr}$  or  $^{141}\text{Ce}$  (3M Co.) randomly assigned. A reference sample of blood was withdrawn from the femoral artery in the following manner. For 10 seconds before injection of microspheres and continuing for a total of 75 seconds, 0.4 ml of blood was withdrawn using a Harvard pump. After the third CBF determination, the rat was killed by disconnecting the ventilator. After decapitation, the whole brain was removed and the pia mater carefully stripped from the brain surface. Samples from left frontal, parietal and occipital cortex and left basal ganglia were placed in pre-tared vials and then reweighed. The blood reference and brain samples were counted by  $\gamma$ -counter (LKB Compugamma). Counts were converted to rCBF by computer program. Only left-sided flows were examined because of altered rCBF responses to changes in  $\text{Paco}_2$  in the right hemisphere secondary to right carotid occlusion (12).

Within-group comparisons were by ANOVA for repeated measures, between-group comparisons for each region were by ANOVA. When the  $F$ -statistic was significant in the above comparisons, Duncan's test was applied post hoc (13);  $P < 0.05$  was considered statistically significant. A  $\text{CO}_2$  response curve for  $\text{Paco}_2$ -rCBF 1 data was generated for each brain region at 1.5 MAC isoflurane anesthesia by using all 24 flow and corresponding  $\text{Paco}_2$  values obtained from the four groups. This was done to assess the



Table 1. Comparative Data For Each Group

	Group 1	Group 2	Group 3	Group 4
Weight (g)	409 ± 10*	428 ± 8	418 ± 4	431 ± 13
Time between injections 1 and 3 (min)	56 ± 4	58 ± 5	52 ± 4	53 ± 3
Isoflurane (%)				
Flow 1	1.89 ± 0.12	2.22 ± 0.05	2.08 ± 0.07	2.10 ± 0.14
Flow 2	4.42 ± 0.28†	4.42 ± 0.25†	4.08 ± 0.15†	4.63 ± 0.21†
Flow 3	4.37 ± 0.23†	4.29 ± 0.20†	3.86 ± 0.07†	4.50 ± 0.18†
PaO <sub>2</sub> (mm Hg)				
Flow 1	272 ± 46	340 ± 47	321 ± 36	360 ± 39
Flow 2	227 ± 34	311 ± 47	315 ± 42	333 ± 28
Flow 3	212 ± 50	296 ± 54	290 ± 42	294 ± 38

\*Mean ± SEM; n = 6 for each group.

†P &lt; 0.001.

Table 2. Reactivity to Carbon Dioxide During 1.5 MAC Isoflurane Anesthesia for Various Brain Regions\*

Region	CBF 1 (1.5 MAC)		
	A	% Slope	r†
Left frontal	-1.103	3.42 ± 0.33‡	0.91 <sup>s</sup>
Left parietal	-1.017	3.27 ± 0.34	0.90 <sup>s</sup>
Left occipital	-0.808	3.05 ± 0.33	0.89 <sup>s</sup>
Left brain ganglia	-1.057	3.94 ± 0.40	0.90 <sup>s</sup>

\*DATA are fitted to the equation of the form  $\ln \text{CBF} = A + \% \text{Slope}/100 \times \text{Paco}_2$ .

†r = correlation coefficient.

‡Mean ± SEM; n = 24

<sup>s</sup>P < 0.001

CO<sub>2</sub> response during 1.5 MAC isoflurane anesthesia to compare our results with previously published results (14) for the CO<sub>2</sub> responsiveness of the rat cerebrovasculature during inhalation anesthesia at normotensive levels. An equation of the form  $\ln \text{CBF} = a + b \cdot \text{Paco}_2$  that best described the  $\text{Paco}_2$ -rCBF relation was determined by least-squares regression analysis.

## Results

Comparative data from the four groups of rats are shown in Table 1. There were no differences in animal weights, duration of experiments, arterial O<sub>2</sub> tensions, or in baseline and deep isoflurane concentrations in any of the four groups.

The data from Table 2 show the reactivity of rat rCBF to changes in  $\text{Paco}_2$  during 1.5 MAC isoflurane/O<sub>2</sub> for the various brain regions examined for  $\text{Paco}_2$ -rCBF 1 data by combining the results from the four groups. All data from the 24 flow measurements for the various rCBF 1 and the corresponding  $\text{Paco}_2$  values were correlated for each brain region. For all regions a steep CO<sub>2</sub> response was seen at 1.5 MAC isoflurane/O<sub>2</sub> anesthesia. The slope of the line

varied between 0.031 and 0.039, i.e., a 3.1–3.9% increase in rCBF/mm Hg increase in  $\text{Paco}_2$  ( $P < 0.001$  for each slope; correlation coefficient  $r = 0.89$ – $0.91$ ).

Data in Table 3 show rCBF at given  $\text{Paco}_2$  levels and mean blood pressures for groups 1–4. For CBF 1 all flow determinations are during normotension at approximately 1.5 MAC inspired isoflurane anesthesia. Comparison of rCBF 1 results for groups 1 and 3 (normocarbica;  $\text{Paco}_2$ , 41 mm Hg) are indistinguishable across the four brain regions examined (ANOVA). In group 2 (initial hypocarbica;  $\text{Paco}_2$ , 19 mm Hg) rCBF 1 values were approximately 50% of those seen with normocarbica in groups 1 and 3 ( $P < 0.01$  vs groups 1 and 3). In group 4 (initial hypercarbica;  $\text{Paco}_2$ , 59 mm Hg) rCBF values were approximately 100% higher than those seen in groups 1 and 3 ( $P < 0.01$  vs groups 1 and 3). The results from CBF 2 for each group were with  $\text{Paco}_2$  values maintained at stable levels but with controlled hypotension initiated by increasing the inspired isoflurane anesthesia to 3.5 MAC. In all groups the mean blood pressure was <50 mm Hg but >45 mm Hg and stabilized at that level for a minimum of 25 minutes before measurement of CBF 2. In groups 1 and 3 (stable normocarbica) there was a statistically insignificant increase in mean rCBF in all regions examined (ANOVA for repeated measures). In group 2 (stable hypocarbica) after institution of controlled hypotension with 3.5 MAC isoflurane anesthesia, rCBF levels were approximately 100% greater than rCBF 1 levels in all regions ( $P < 0.01$  vs CBF 1). In group 4 (stable hypercarbica) rCBF decreased 27–33% when mean blood pressure was 40% below baseline levels ( $P < 0.01$  vs CBF 1). For CBF 3 mean blood pressure was held constant at 3.5 MAC isoflurane and  $\text{Paco}_2$  was either increased or decreased in each group as listed. A minimum of 25 minutes elapsed at the new CO<sub>2</sub> level before CBF 3 was measured. Despite a decrease in CO<sub>2</sub> in groups 1 and 4 or an increase in CO<sub>2</sub> in groups 2 and 3, there

Table 3. rCBF at Given Levels of  $P_{aCO_2}$  and Mean Blood Pressure for Groups 1 to 4

	$P_{aCO_2}$	Mean BP	Frontal	Parietal	Occipital	B. ganglia
Group 1						
CBF 1	41.1 $\pm$ 1.1*	80.3 $\pm$ 1.4	1.35 $\pm$ 0.11	1.37 $\pm$ 0.11	1.60 $\pm$ 0.16	1.77 $\pm$ 0.14
CBF 2	40.0 $\pm$ 1.2	46.8 $\pm$ 0.7†	1.51 $\pm$ 0.16	1.78 $\pm$ 0.13	1.98 $\pm$ 0.13	2.33 $\pm$ 0.14
CBF 3	22.5 $\pm$ 1.7†	46.0 $\pm$ 0.5†	1.59 $\pm$ 0.18	1.83 $\pm$ 0.26	2.06 $\pm$ 0.32	2.35 $\pm$ 0.38
Group 2						
CBF 1	18.9 $\pm$ 1.3	88.7 $\pm$ 3.8	0.64 $\pm$ 0.05	0.66 $\pm$ 0.06	0.81 $\pm$ 0.06	0.83 $\pm$ 0.15
CBF 2	17.4 $\pm$ 1.1	46.0 $\pm$ 0.9†	1.22 $\pm$ 0.11†	1.26 $\pm$ 0.09†	1.42 $\pm$ 0.11†	1.66 $\pm$ 0.21†
CBF 3	42.3 $\pm$ 2.9†	45.5 $\pm$ 0.3†	1.35 $\pm$ 0.13†	1.43 $\pm$ 0.13†	1.55 $\pm$ 0.15†	1.62 $\pm$ 0.22†
Group 3						
CBF 1	41.3 $\pm$ 2.1	85.5 $\pm$ 2.6	1.34 $\pm$ 0.14	1.49 $\pm$ 0.13	1.61 $\pm$ 0.23	1.80 $\pm$ 0.33
CBF 2	36.7 $\pm$ 2.3	48.0 $\pm$ 0.6†	1.81 $\pm$ 0.27	1.95 $\pm$ 0.29	2.13 $\pm$ 0.29	2.28 $\pm$ 0.21
CBF 3	57.7 $\pm$ 5.5†	47.7 $\pm$ 0.7†	2.01 $\pm$ 0.24‡	2.15 $\pm$ 0.25‡	2.43 $\pm$ 0.27‡	2.41 $\pm$ 0.24
Group 4						
CBF 1	58.5 $\pm$ 2.4	81.7 $\pm$ 3.2	2.72 $\pm$ 0.28	2.61 $\pm$ 0.26	2.80 $\pm$ 0.27	3.72 $\pm$ 0.37
CBF 2	56.4 $\pm$ 1.8	47.7 $\pm$ 0.8†	1.83 $\pm$ 0.19†	1.91 $\pm$ 0.19†	2.03 $\pm$ 0.20†	2.02 $\pm$ 0.21†
CBF 3	34.2 $\pm$ 2.5†	47.7 $\pm$ 0.6†	1.86 $\pm$ 0.16†	1.88 $\pm$ 0.16†	2.19 $\pm$ 0.27‡	2.15 $\pm$ 0.23†

\*Mean  $\pm$  SEM;  $n = 6$  for each group. Results are expressed in  $\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ .† $P < 0.01$  vs CBF 1.‡ $P < 0.05$  vs CBF 1.

was no significant difference in rCBF in any region for any group for the two  $\text{CO}_2$  levels compared within each group, i.e.,  $\text{CO}_2$  responsiveness of the rat cerebrovasculature was lost at 3.5 MAC isoflurane/ $\text{O}_2$  anesthesia when mean blood pressure was 46–48 mm Hg.

## Discussion

Using the radioactive microsphere technique we have examined rCBF in the rat during isoflurane/ $\text{O}_2$  anesthesia at 1.5 MAC inspired concentration and during controlled hypotension at 3.5 MAC isoflurane/ $\text{O}_2$  anesthesia. We have also examined the  $\text{CO}_2$  responsiveness of the cerebral vasculature at 1.5 and 3.5 MAC. We have attempted to design the experimental model so that mean blood pressures and  $P_{aCO_2}$  values during the normotensive controls and during periods of controlled hypotension have clinical relevance despite use of a rat model. Examination of the literature suggests that the 1.5 MAC isoflurane anesthesia we used is a deeper level of baseline anesthesia than that used by many investigators when determining control CBF values in rat models (15,16). We consulted the Harvard Bioscience catalog (17) (a compendium of normal rat physiologic values) to arrive at a normal mean blood pressure of 92 mm Hg in the adult rat. Higher control mean blood pressure values published in various papers (15,16) are usually obtained after the animal has been invasively monitored, paralyzed, and ventilated with  $\text{N}_2\text{O}/\text{O}_2$  analgesia. Our baseline flows during normocarbica agree well with those published by Lauritzen (14) for rats

anesthetized with 1.5 MAC halothane/ $\text{O}_2$  anesthesia and, like Lauritzen, we have obtained a similar  $\text{CO}_2$  response curve for all regions examined of 3.1–3.9% increase in rCBF/mm Hg increase in  $P_{aCO_2}$  (Table 2). We also deliberately chose to decrease mean blood pressure below the published lower limits of the autoregulatory threshold for CBF in the rat anesthetized with an inhalation anesthetic (18,19). The published values for the lower limit of the threshold are stated to be 50–70 mm Hg. We elected to investigate rCBF below the lower limit of the autoregulatory threshold because we consider this information to be clinically important because the neurosurgeon frequently requests that the mean blood pressure be reduced below this level to facilitate clipping of a cerebral aneurysm. In addition, Warner et al. (20) suggest that approximately 3–4% inspired isoflurane concentration is necessary to assure burst suppression in the rat. This is a higher inspired concentration than that necessary for a similar effect in humans (4).

Examination of the data in Table 3 reveals the effect of the change in rCBF when 3.5 MAC inspired isoflurane anesthesia was initiated to induce controlled hypotension at stable  $\text{CO}_2$  levels in each group. From CBF 1 to CBF 2 the isoflurane concentration was increased to 3.5 MAC to decrease the mean blood pressure to  $<50$  mm Hg in each group. The isoflurane concentration and mean blood pressure were stable for a minimum of 25 minutes before determination of CBF 2. We demonstrated that despite a 40% decrease in mean blood pressure during normocarbica (groups 1 and 3), rCBF was increased minimally above baseline values. There was a 100% increase in rCBF in group 2 (initial hypocarbica;  $P_{aCO_2}$ ,

17 mm Hg). This indicates that the marked vasodilatory effects of 3.5 MAC isoflurane anesthesia in the face of a 40% decrease in blood pressure overwhelm the vasoconstrictive effects of hypocarbia. In group 4 (initial hypercarbia;  $Paco_2$ , 56 mm Hg), rCBF decreased significantly during 3.5 MAC isoflurane anesthesia. In this group, regional flows decreased approximately 30% when mean blood pressure was 40% below baseline levels, implying pressure passive flow during isoflurane anesthesia in the presence of hypercarbia.

Our results corroborate the work of others who found CBF unchanged or increased when the concentration of isoflurane was increased to induce controlled hypotension in the presence of hypocarbia or normocarbia (1-4).

Comparisons of rCBF 2 and 3 in each group demonstrate loss of  $CO_2$  response of the rat cerebral vasculature at 3.5 MAC isoflurane anesthesia when mean blood pressure was <50 mm Hg. This was true in all regions of the brain in each group regardless of whether or not the  $CO_2$  was raised or lowered from the previous value present during CBF 2. These results differ from the findings of Artru (7), who showed that in the dog model there was a 50% preservation of the increase in total CBF/mm Hg increase in  $Paco_2$  during hypotension to a level of blood pressure similar to that in the present study, but with an inspired concentration of isoflurane (2.5-4.3%) lower than we used. There are multiple differences between the two studies: different animal models, different techniques for measurement of CBF, the absence of  $N_2O$  in our study,  $CO_2$  changes over a shorter time period in our study, and measurement of rCBF in our model as opposed to total CBF in Artru's model. We also investigated  $CO_2$  response during hypercarbia. The major difference between the two studies, however, may relate to our attempt to deliberately decrease mean blood pressure to below the autoregulatory threshold with a high inspired isoflurane concentration, whereas in Artru's study mean blood pressure was probably reduced only to the level of the autoregulatory threshold (10). Although this difference in experimental protocols was deliberate, it also resulted in the rats in our study having slightly lower mean blood pressures during controlled hypotension. This may have contributed to the loss of  $CO_2$  responsiveness by the cerebral vasculature as demonstrated in our study. The loss of rCBF responsiveness to changes in the level of  $Paco_2$  seen in our experiments is similar to findings in other laboratories for halothane (21,22). Absence of a direct response of CBF to increases in  $Paco_2$  has been demonstrated with infusion of intravenous agents

such as sodium nitroprusside and trimethaphan (8) and nitroglycerin (9) during halothane anesthesia.

Criticisms of our model include the fact that the left ventricular line was placed through the right common carotid, which necessitated ligation of this vessel. We have not presented data from the right hemisphere because of altered  $CO_2$  response when one carotid has been ligated (12). Ligation of the right common carotid does not alter the  $CO_2$  response of the cerebral vasculature in the left hemisphere (12). We have shown a moderately steep response to rCBF to  $Paco_2$  changes at 1.5 MAC in the left hemisphere, which agrees with previous work for  $CO_2$  responses in the rat with 1.5 MAC halothane/ $O_2$ , in a model in which the right carotid is not ligated (14). This suggests our model is adequate for investigation of  $CO_2$  responses of rCBF. In control experiments, we demonstrated stable rCBF at constant  $CO_2$  and mean BP and an intact  $CO_2$  response for up to three flow determinations during isoflurane/ $O_2$  anesthesia. We have used a relatively large number of microspheres (500,000/injection) to permit assessment of rCBF. Others used a similar number of microspheres/injection without noticeable deterioration of the animal preparation (23,24). We observed no deterioration of the rat's physiologic status when comparing mean blood pressure and arterial blood gas data before and after injection.

In conclusion, using a rat model with rCBF determined by the radioactive microsphere technique, we have demonstrated a 3.1-3.9% increase in rCBF/mm Hg increase in  $Paco_2$  during 1.5 MAC isoflurane/ $O_2$  anesthesia. During controlled hypotension to a level below the autoregulatory threshold for cerebral blood flow in the rat, 3.5 MAC inspired isoflurane anesthesia resulted in loss of the  $CO_2$  response of the cerebral vasculature. In addition, and perhaps most important, during controlled hypotension with 3.5 MAC isoflurane anesthesia, rCBF was maintained at levels that approximated those seen with 1.5 MAC isoflurane anesthesia when rats had normocarbic blood gases. These results show rCBF is well maintained in normal cerebral tissue when mean blood pressure is decreased to below the autoregulatory threshold during controlled hypotension with deep isoflurane anesthesia.

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## Effects of Aerosolized and/or Intravenous Lidocaine on Hemodynamic Responses to Laryngoscopy and Intubation in Outpatients

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LAURITO CE, BAUGHMAN VL, BECKER GL, POLEK WV, RIEGLER FX, VADE BONCOUER TR. Effects of aerosolized and/or intravenous lidocaine on hemodynamic responses to laryngoscopy and intubation in outpatients. *Anesth Analg* 1988;67:389-92.

*A randomized, double-blind study was carried out on 40 unpremedicated, ASA I-II adult surgical outpatients to assess the effects of aerosolized lidocaine, intravenous lidocaine, both, or neither, on circulatory responses to laryngoscopy and intubation. Lidocaine (4 mg/kg) or saline was given by nebulizer in the holding area beginning at -15 minutes. The patient underwent a standardized induction of anesthesia that included IV curare (3 mg) and O<sub>2</sub> by facemask at minute 2, followed by IV thiopental (5 mg/kg) and succinylcholine (1.5 mg/kg) at minute 5. Lidocaine (2 mg/kg) or saline was given by IV push at minute 4. Laryngoscopy was begun at 5 minutes and continued for 45 seconds before intubation. Heart rate and systolic, diastolic, and mean blood pressures were automatically recorded at 1-minute intervals from 0 to 11 minutes. The four treat-*

*ment groups included: group 1, aerosolized and IV saline; group 2, aerosolized saline, IV lidocaine; group 3, aerosolized lidocaine, IV saline; and group 4, aerosolized and IV lidocaine. There were no differences among the four treatment groups (n = ten per group) in any of the four hemodynamic variables before laryngoscopy and intubation. Within each group, after intubation all four hemodynamic variables increased significantly over the corresponding baseline values for that group. However, the maximum values attained after intubation did not differ significantly among the four treatment groups for any of the four hemodynamic variables, whether those maxima were expressed as absolute values or as a percentage of baseline. Having found no difference in the effects of aerosolized and/or intravenous lidocaine and saline placebo on hemodynamic response to laryngoscopy and intubation in adult surgical outpatients using a rigidly standardized protocol, it is recommended that such usage of lidocaine be abandoned.*

**Key Words:** INTUBATION, TRACHEAL—lidocaine use. ANESTHETICS, LOCAL—lidocaine.

Laryngoscopy and tracheal intubation are potent stimuli that increase heart rate and blood pressure (1-3), particularly if laryngoscopy takes as long as 45 seconds (4). Laryngoscopy alone generates essentially the same pressor response and sympathoadrenal response as does laryngoscopy followed by intubation (5). Measures that effectively blunt these responses including heavy premedication, high-dose narcotics, deep inhalational anesthesia, and potent vasoactive drugs (4,6,7) also commonly prolong re-

covery time and can lead to cardiovascular complications (6,7) and thus are contraindicated in patients scheduled for brief surgical procedures. Lidocaine, which avoids these problems, has also been used to blunt hemodynamic stimulation during laryngoscopy (8). Although the efficacy of lidocaine treatment in this setting has been questioned (1,9), definitive conclusions have been precluded by lack of comparability among existing studies conducted mainly in premedicated patients with widely varying baseline medical status and duration of laryngoscopy (1,2,5, 8-10).

Our study has focused specifically on unpremedicated, generally healthy adult patients undergoing outpatient surgery. In addition to representing a more medically homogenous population, such pa-

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Table 1. Effect of Lidocaine and/or Saline on Hemodynamic Responses to Laryngoscopy and Intubation\*

	Nebulized drug/Intravenous drug			
	S/S	S/L	L/S	L/L
Heart rate				
Baseline (beats/min)†	79 (4)	71 (4)	77 (5)	76 (5)
Maximum (beats/min)‡	117 (3)	108 (8)	113 (6)	114 (3)
Maximum (%)§	152 (9)	153 (8)	150 (10)	156 (11)
Mean blood pressure				
Baseline (mm Hg)	101 (5)	95 (3)	102 (2)	96 (4)
Maximum (mm Hg)	141 (6)	130 (7)	142 (6)	136 (6)
Maximum (%)	141 (7)	143 (8)	139 (5)	142 (6)
Systolic blood pressure				
Baseline (mm Hg)	131 (7)	127 (3)	129 (3)	128 (5)
Maximum (mm Hg)	170 (6)	163 (10)	176 (7)	168 (7)
Maximum (%)	130 (7)	136 (7)	138 (5)	132 (5)
Diastolic blood pressure				
Baseline (mm Hg)	75 (5)	73 (2)	76 (2)	73 (3)
Maximum (mm Hg)	108 (5)	102 (6)	111 (5)	107 (5)
Maximum (%)	145 (6)	142 (8)	145 (5)	147 (6)

\*Values are given as mean (SEM). Abbreviations: S, saline; L, lidocaine.

†Pre-intubation baseline = average of 0 to 3-min values.

‡Post-intubation maximum = highest of 5 to 8-min values.

§Maximum expressed as percentage of baseline.

tients may be more likely to be cared for by residents early in their clinical training period and therefore to experience a stronger stimulus in the form of prolonged laryngoscopy. We have compared the effectiveness of aerosolized and/or intravenous lidocaine and placebo for the control of hemodynamic responses to laryngoscopy and endotracheal intubation.

## Methods

Following approval by our investigational review board and receipt of informed consent from our patients, 40 ASA I and II patients were each randomly assigned to one of four treatment groups. Within a span of 15 minutes, as detailed below, each patient received either lidocaine or placebo by nebulizer, followed by lidocaine or placebo by IV push. Both patient and anesthesiologist were unaware of the contents of nebulizer and syringe.

Procedures for study drug administration and for anesthetic induction were rigorously standardized. Nebulized lidocaine (4 mg/kg) or an equivalent volume of saline was given over a 10-minute period in the holding area. The patient was instructed to breathe the aerosolized mist through a mouthpiece. The patient immediately entered the OR, where automated recordings (Datascopes) of heart rate (HR) and systolic (SBP), diastolic (DBP), and mean (MBP) blood pressures were initiated (= 0 min) and repeated at

1-minute intervals thereafter. At 2 minutes curare (3 mg) was given and followed with O<sub>2</sub> by mask. At 4 minutes either lidocaine (2 mg/kg) or saline was given intravenously, followed immediately by thiopental (5 mg/kg) and then succinylcholine (1.5 mg/kg). Laryngoscopy was begun at 5 minutes and maintained for exactly 45 seconds before passage of the endotracheal tube followed by mechanical ventilation with either 1.5% isoflurane or 2% enflurane in 70% N<sub>2</sub>O/30% O<sub>2</sub> at 6 L/min. The patient was left undisturbed for an additional 6 minutes of hemodynamic recordings, at which point the study was terminated. The same blood pressure machine was used on all patients to eliminate variability in determining blood pressure or heart rate and recording data. Our induction technique paralleled the drug doses and sequence frequently used in our outpatient anesthesia department.

## Results

The four groups were comparable in terms of age, sex, weight, and ASA classification. None were taking cardioactive or respiratory medication. Pre- and postintubation values for HR, SBP, DBP, and MBP in the four treatment groups are shown in Table 1. There were no statistically significant differences among the groups for any of the measured variables before intubation ( $P > 0.05$  by ANOVA). Heart rate, SBP, DBP, and MBP all increased significantly above

baseline levels after intubation in each of the four groups ( $P < 0.05$  by paired  $t$ -test). However, postintubation maximal values did not differ significantly among the four treatment groups, whether compared as absolute values or as percentage increases from baseline.

## Discussion

Several studies have looked at the efficacy of intravenous and topical oropharyngeal lidocaine as an agent to blunt the hypertensive and tachycardic response to laryngoscopy and intubation. The results of these studies have been contradictory, probably because of differences in study protocol (i.e., patient population, premedication, depth of anesthesia, method of lidocaine delivery, dose of lidocaine, duration of laryngoscopy, interval between lidocaine administration and laryngoscopy, and method of stress evaluation).

Our study examined the cardiovascular response of unpremedicated, healthy ASA I-II outpatients subjected to prolonged laryngoscopy before intubation. We chose this patient population to evaluate a homogenous group of patients who did not have medical problems, did not require concurrent medication (i.e.,  $\beta$ -blockers, calcium channel blockers, digoxin, nitroglycerine), and did not receive significant preoperative sedation. We also selected this group because they may frequently be cared for by junior residents or medical students, which increases the potential for prolonged laryngoscopy. Laryngoscopy was maintained for 45 seconds before intubation to provide a maximal stimulus. Stoelting (4) demonstrated near maximal pressor response at 45 seconds of laryngoscopy, with little to no additional increase with sustained laryngoscopy.

We administered lidocaine by aerosol and/or intravenously to determine whether topical, intravenous, or the combination of topical plus intravenous lidocaine was superior in blunting the cardiovascular response to laryngoscopy and intubation. Aerosolized lidocaine was selected rather than intratracheal lidocaine to avoid two laryngoscopies, which has confused data in several studies. Aerosolized lidocaine has been shown to provide good topical anesthesia (2,8). When administered 5 to 15 minutes before airway instrumentation, 4 mg/kg nebulized lidocaine (11) produce maximal arterial blood levels of  $<2 \mu\text{g/ml}$ . We injected IV lidocaine (2 mg/kg) 1 minute before laryngoscopy. This dose produces arterial blood levels of 6–7.5  $\mu\text{g/ml}$  in 1 minute (12,13), with rapid decline to 2–3  $\mu\text{g/ml}$  at 5 minutes (12). Our largest lidocaine dose (group 4) was 4 mg/kg by

aerosol followed by a 2 mg/kg IV bolus. This dose is sufficient to cause a high arterial blood level, in an attempt to obtain a maximal effect from the medication, without producing toxic levels (12–14).

Our data confirm the work of both Chraemmer-Jorgenson et al. (1) and Derbyshire et al. (9). The former investigators found no beneficial effect of intravenous lidocaine (1.5 mg/kg) given 2 minutes before rapid sequence laryngoscopy and intubation. Derbyshire et al. (9) reported that topical lidocaine did not blunt the increase in blood pressure, in heart rate, or in plasma catecholamine levels after laryngoscopy/intubation.

Venus et al. (7) reported significantly greater cardiovascular stability after laryngoscopy and intubation in patients pretreated with aerosolized lidocaine (240 mg) than that in a control group that received aerosolized saline. To provide maximal stimulus, Venus et al. (7) maintained laryngoscopy for 60 seconds. Other than morphine premedication (1 mg/10 kg) and the fact that they studied inpatients, their protocol was similar to ours. We are not able to explain the difference between their results and ours unless there was a difference in delivery of aerosolized lidocaine between their patients and ours. We used standard respiratory therapy equipment and generally accepted administration methods.

Previous studies also differ from ours in two important ways: 1) most patients received premedication including benzodiazepines and/or narcotics and, 2) there was no consistent approach to the duration of laryngoscopy; many intubations were performed after rapid sequence induction of anesthesia and therefore caused less cardiovascular stress.

In summary, our study examined the hemodynamic responses of unpremedicated healthy patients subjected to prolonged laryngoscopy, a condition expected to evoke a maximum hemodynamic change. We found no advantage to the use of lidocaine (aerosolized, IV, or both) compared to placebo. In each of our groups the stimulus of laryngoscopy and tracheal intubation significantly increased heart rate and blood pressure, yet we found no differences in the absolute or relative extent of these elevations between the various treatment and control groups. Our results suggest that the administration of lidocaine before laryngoscopy in healthy adult patients affords no protection to the cardiovascular system.

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## Clinical Reports

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# Combined Anesthetic- and Stress-Induced Malignant Hyperthermia in Two Offspring of Malignant Hyperthermic-Susceptible Parents

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**Key Words:** HYPERTHERMIA—malignant.

For the past 18 years we have been observing an unusual malignant hyperthermic-susceptible (MHS) family (pedigree NNB, Fig. 1). Initially the only individual in the family to have had an anesthetic-induced malignant hyperthermic (MH) reaction was the proband, C.B. As the years passed, however, three other members suffered pyrexial anesthetic-induced reactions (the proband's mother, C.B.L., brother, J.B., and second cousin once removed B.T.). Additionally, second nonanesthetic induced reactions were sustained by two members of this family (the proband, C.B., and her brother, J.B.) and in each, this second crisis was fatal. We propose, therefore, to describe the genetic history and the individual reactions suffered by members of this family in detail and then to discuss the interlocking roles of the various triggering factors.

The genetic history of this family (Fig. 1) was unusual in that two apparently malignant hyperthermia-susceptible individuals married each other. Thus the mother had an anesthetic-induced reaction and a muscle biopsy positive for MH, while one of the father's collateral relatives (his second cousin once removed, B.T.) had a fatal, febrile anesthetic-related reaction. Furthermore, the father, paternal grandfather, and paternal great-grandmother all had persistently elevated creatine kinase levels. It may be, therefore, that the proband and her brother were homozygous for MH, which would help explain the

severity of the terminal reactions suffered by these two siblings.

## Case Histories

### C.B. (Proband)

*December 2, 1964.* The proband was a 4-year-old, very muscular Caucasian female who was admitted to hospital for a cystoscopy because of abdominal pain due to a renal tract infection. The child was otherwise in good health. Premedication consisted of intramuscular pentobarbital 40 mg and scopolamine 0.2 mg. On arrival in the operating room she was markedly apprehensive.

Anesthesia was induced with halothane at 1135 hours. During and after induction, laryngeal stridor occurred. Throughout the 25-minute procedure, the heart rate (HR) ranged from 128 to 125 beats/min, and the respiratory rate (RR) varied from 60 to 65 breaths/min.

On arrival in the postanesthetic recovery room (PAR) the heart rate was 160 beats/min and bounding, RR was 48 breaths/min, and the skin was dusky and very warm. Oxygen was given by mask. Fifteen minutes later, at 1215 hours, the rectal temperature (Tr) rose to 105.6°F. Twitching and definite cyanosis developed, for which thiopental 40 mg was given.

By 1250 hours, her temperature was above 108°F. A hypothermia blanket was, therefore, applied. Thirty-five minutes later the Tr had decreased to 101°F. The blood pressure (BP) at this time was 76/30 mm Hg. Shortly thereafter hydrocortisone 50 mg and norepinephrine 2 mg were given. This led to an increase in the BP to 100/40 mm Hg and a decrease in Tr to 95.6°F. Nearly 3 hours after entering the PAR the reaction appeared to be recrudescing in that the

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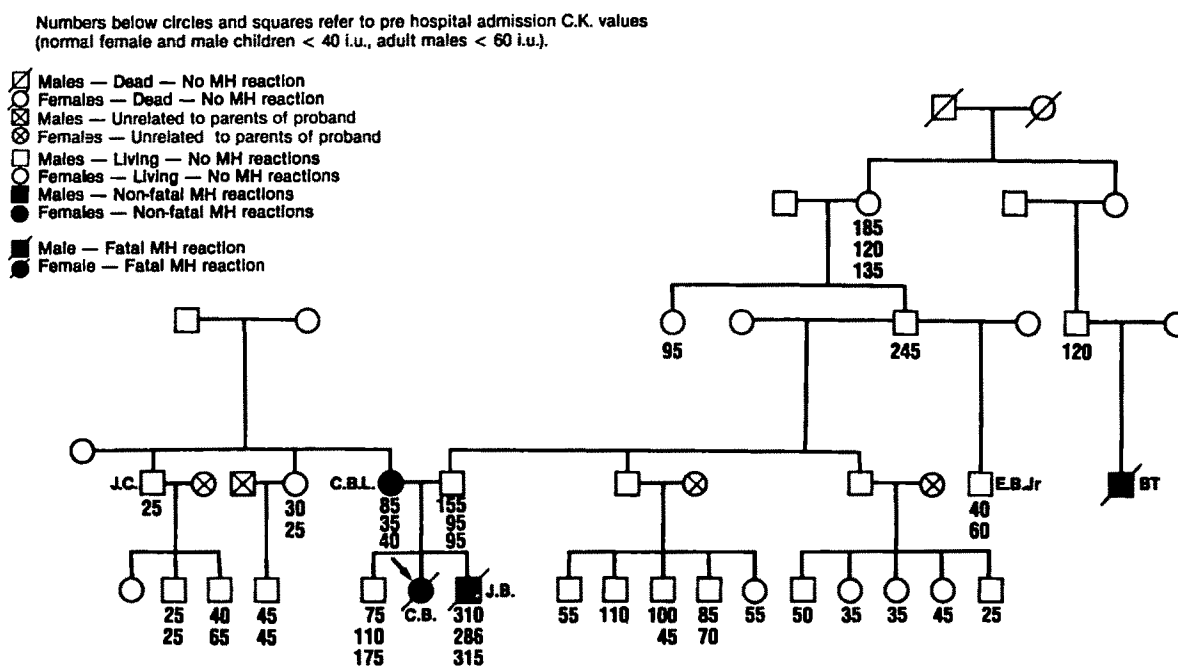


Figure 1. Pedigree NNB.

Tr had risen to 100.2°F and the abdominal muscles appeared tensed and distended.

About 1 hour later the urine was dark and decreased in volume, the Tr continued to rise to 101.5°F, and the BP to 110/60 mm Hg. Pentobarbital 15 mg, diphenylhydantoin 50 mg, and hydrocortisone 50 mg were administered. By 1815 hours, the BP was 112/64 mm Hg, HR 130 beats/min, RR 34 breaths/min, and Tr 97.6°F. At 2215 hours, C.B. was transferred to the ward with all vital signs normal and responding to external stimuli. The retrograde pyelogram suggested right uretero pelvic obstruction with hydronephrosis.

**March 3, 1965.** C.B. was readmitted for exploratory surgery to determine the cause of the hydronephrosis. Preoperative HR was 112 beats/min. Pre-medication comprised pentobarbital 35 mg and atropine 0.15 mg.

At 0805 hours, induction with intubation was performed with cyclopropane, during which persistent low grade laryngeal obstruction and cyanosis were observed. Anesthesia was maintained with 1% halothane and nitrous oxide:oxygen (N<sub>2</sub>O:O<sub>2</sub>) = 2:2 L/min. AT 0855 hours, HR was 135 beats/min, BP 64/30 mm Hg, and RR 23 breaths/min. Cyanosis and muscle rigidity developed. When the concentration of halothane was increased the blood pressure dropped sharply. One hundred ml of blood was transfused. Rectal temperature had risen to 101.4°F and so surgery was cancelled. Ice packs were applied, another 100 ml of whole blood was given, and an

aspirin suppository was inserted. By 0950 hours, the Tr was 105.2°F, HR 197 beats/min, BP 140/70 mm Hg, and RR 35 breaths/min. As the child was awakening, she was extubated and 3 L/min of oxygen by mask was instituted.

At 1000 hours, C.B. was sent to the PAR packed in ice with an HR of 144 beats/min, RR 32 breaths/min, and Tr 100.6°F. At 1230 hours the patient was discharged from the RR with all vital signs normal.

**December 4, 1965.** Between 0800 and 0900 hours, C.B. developed flu-like symptoms with a low grade fever and failure to void over a 10–12-hour period. That evening, coughing and wheezing occurred. Her mother (C.B.L.) applied Vicks Vapo Rub to the chest. Almost immediately the Tr rose to 108°F and convulsions occurred associated with extreme rigidity of the legs. An ambulance was called. In the ambulance C.B. became deeply cyanotic, and board-like rigidity developed. She was declared dead shortly after admission to hospital.

#### J.B. (Brother of Proband)

**November 1, 1973.** J.B. was referred to the Malignant Hyperthermia Investigation Unit (MHIU) at the Toronto General Hospital (TGH) at age 8 years for skeletal muscle biopsy for diagnosis of MH and for repair of a chronically subluxating right knee joint. He was very muscular and had hypermobility of both

knee joints, particularly the right. He complained of "growing pains" in his legs and exhibited moderate thoracic kyphoscoliosis with marked lumbar lordosis, slight winging of the scapula, and hypertrophy of muscles of the extremities. He had a hyperactive personality and multiple allergies. Other aspects of his history and physical examination were normal. No previous anesthetics had been given. The admitting creatine kinase (CK) was 265 IU (normal < 40 in male children).

Induction of anesthesia was performed with N<sub>2</sub>O:O<sub>2</sub> 6:4 L/min for 2 minutes, then 2 ml Innovar was injected followed by 10 mg diazepam. Intubation was easily performed after spraying the vocal cords with 5% cocaine.

Anesthesia was maintained with N<sub>2</sub>O:O<sub>2</sub> 6:4 L/min plus repeated doses of thiopental and fentanyl. During the first hour of anesthesia vital signs were normal. During the next hour and 40 minutes of anesthesia, the HR increased to 150 beats/min, the systolic BP increased to 138 mm Hg, while the Tr fell to 34.7°C.

In the RR, violent shivering occurred, the HR varied between 120 and 140 beats/min, the BP ranged between 100–120/55–70 mm Hg, and Tr increased to 38°C. Thirty minutes after admission to the RR, Pao<sub>2</sub> = 60 mm Hg, Pao<sub>2</sub> = 230 mm Hg, pH = 7.24, and base deficit = -2.5 mEq/L. On return to the ward, convalescence was uneventful.

Skeletal muscle biopsy revealed a caffeine-halothane contracture (CHC) test strongly positive for MH (1,2), with the caffeine-specific concentration (CSC, the concentration of caffeine in mM required to raise the resting tension of a skeletal muscle fascicle by one gram) = 0.48 mM (normal > 4.1 mM), the caffeine-specific concentration-halothane (CSC-H, the concentration of caffeine in mM required to raise the resting tension of a skeletal muscle fascicle by one gram in the presence of 1.0 volume % halothane) = 0.23 mM (normal > 1.05 mM), and 1% halothane contracture = 0.3 gm% (normal < 0.1 gm) (1). Microscopic examination of muscle sections revealed increased variation in fiber size, targetoid cells, and subsarcolemmal filamentous bodies (3–5). The ratio of type I/II fibers was normal, 0.5. Maximum postsurgical CK on the second postoperative day was 470 IU.

*March 21, 1985.* On his twenty-first birthday, J.B. attended his birthday party at which he ingested both alcohol and cocaine. He was described by his girlfriend as being in an extremely excited frame of mind. Late in the evening he was found in his car by his girlfriend, was apparently difficult to understand, complaining of not feeling well, appearing quite

sweaty, and feeling hot. She drove J.B. to a hospital emergency room at 0315 hours and on returning to the car with assistance she found J.B. collapsed and unresponsive. The muscles of his legs were so rigid that he could not be got into a wheelchair.

J.B.'s past MH history was unknown to the attending staff in the emergency room. He was not wearing a Medic-Alert bracelet, and the girlfriend did not know he had MH. He was semiconscious so that no information could be clearly elicited from him. He was violently hyperventilating (48 breaths/min), agitated with pupils round, equal, and reactive to light. The jaw and the lower extremities were rigid and arched. While the skin was mottled, clammy, and cool, the Tr was 107°F. Blood pressure was 108/64 mm Hg. At 0326 hours, NaHCO<sub>3</sub> 44.6 mEq was infused and nasal oxygen was given. The head of the bed was raised and attempts were made to get the patient to ventilate more slowly by having him breathe into a paper bag. The paper bag treatment was rapidly followed by respiratory arrest. At 0330 hours a seizure occurred. Serum potassium (K) was 5.9 mEq/L, blood CK 1510 IU (normal < 280 IU), blood lactic acid 660 mg/dl, Pao<sub>2</sub> 79.1 mm Hg, pH 6.85, Paco<sub>2</sub> 101.3 mm Hg, and base excess -19.8 mEq/L. A cardiac monitor revealed ventricular tachycardia for which lidocaine 100 mg was given. At 0335 hours an endotracheal tube was inserted against some resistance with the aid of diazepam 5 mg and cardiopulmonary resuscitation was commenced. Between 0336 and 0352 hours, atropine 1.0 mg, diazepam 5 mg, hydrocortisone 100 mg, naloxone 0.2 mg, procainamide 500 mg, and NaHCO<sub>3</sub> 133.8 mEq were given. Cardioversion at 400 watt-seconds was attempted unsuccessfully three times. Pao<sub>2</sub> was 216.4 mm Hg, pH 6.93, Paco<sub>2</sub> 58 mm Hg, and base excess -22 mEq/L at 0400 hours. Between 0405 and 0443 hours, the following drugs were given: NaHCO<sub>3</sub> 178.4 mEq, furosemide 120 mg, procainamide 250 mg, naloxone 1.5 mg, dopamine 800 mg in 500 cc IV fluid, and dantrolene sodium 80 mg. At 0447 hours a faint femoral pulse was obtained. Two further doses of 44.6 mEq of NaHCO<sub>3</sub> were given. In spite of continued ventilation with 10 L/min of oxygen by endotracheal tube and Ambubag, Pao<sub>2</sub> was 72.5 mm Hg, pH 7.31, Paco<sub>2</sub> 63 mm Hg, and base excess +3.9 mEq/L at 0455 hours. Because the pupils had become and remained fixed and dilated, and as pulmonary edema was present with a straight line ECG, the patient was declared dead at 0525 hours.

Postmortem pathologic examination revealed marked rigor mortis of both lower extremities, hypertrophy of calf and thigh muscles, marked scoliosis of the spine, frothy material in the trachea and bronchi,

edema and hemorrhage in both lungs, edema of the brain, mild congestion with brownish discoloration of the liver, congestion of the spleen, haemorrhagic areas in the thymus and congestion of both kidneys.

Postmortem biochemical examinations were as follows: urine cocaine 9.3  $\mu\text{g/ml}$ , gastric fluid cocaine 105.3  $\mu\text{g/13 ml}$ , blood cocaine negative, liver cocaine negative; urine benzylconine (a metabolite of cocaine) positive, vitreous benzylconine negative; blood ethanol 0.07%; brain ethanol 0.08%, vitreous CK 2,000 IU/L, vitreous lactic acid 60 mg/dl, urine imipramine, desipramine, and phenothiazine, negative.

#### *C.B.L. (Mother of Proband)*

In 1969 at age 34 years, C.B.L. was admitted to hospital for a hysterectomy. A repair of a Bartholin cyst in 1960 using cyclopropane had been uneventful. She exhibited joint hypermobility, extreme muscularity, and had repeated episodes of paroxysmal palpitations and allergy to penicillin. Blood pressure was 150/92 mm Hg. Other aspects of her history and physical examination were normal. The ECG was normal except for low voltage in limb leads. Laboratory data were normal.

Induction of anesthesia was with thiopental, succinylcholine, and halothane. The jaw muscles failed to relax and the temperature increased 3°F. Halothane was, therefore, discontinued, and recovery ensued without further treatment.

In July 1974, at our institution an anesthetic for a skeletal muscle biopsy was given as described for her son. Both anesthesia and recovery were uneventful. The CHC test was positive for MH but less so than that of her son, J.B. (CSC was 3.35 mM, CSC-H 0.34 mM, and halothane contracture 0.00 gm%). Microscopy was normal except for excessive numbers of internal nuclei. On the first postoperative day, the serum CK increased to 310 IU.

#### *B.T. (Second Cousin Once Removed of Proband)*

B.T., a 24-year-old muscular white male, caught his hand in a press on April 19, 1974. The resulting pressure crushed the radial side of the right hand, necessitating emergency surgery. He had had a previous tonsillectomy. Physical examination was normal. An initial anesthetic for this injury with thiopental, succinylcholine infusion, halothane, nitrous oxide and oxygen, lasted 4 hours and was uneventful.

In an effort to obtain a more functional result, further surgery was proposed for the May 20, 1974.

At that time, B.T. denied any allergies and did not mention a family history of malignant hyperthermia. Premedication comprised meperidine 50 mg and atropine 0.6 mg.

Induction was accomplished at 0900 hours with thiopental 250 mg and succinylcholine 50 mg. Intubation was performed without difficulty. Anesthesia was maintained with halothane, 50% N<sub>2</sub>O and 50% O<sub>2</sub>. Except for occasional assistance, the patient breathed spontaneously. Initially his color, BP, and HR were all within normal limits. However, from about 30 minutes after induction, the respiratory rate appeared intermittently to be in excess of 30 breaths/min.

While bandaging the wound at 1140 hours, the surgeon noticed extreme warmth of the skin and marked stiffness of the back muscles. The anesthetist decided to keep the patient in the operating room for some extra time because he was looking slightly pale. A few moments later the BP dropped to 90/60 mm Hg and oxygen was restarted. Over the next few minutes, the BP increased to 110/70 mm Hg and the patient's color improved. However respirations became more rapid and labored and cyanosis developed. By 1215 hours, no pulse could be palpated. Reintubation was performed and external cardiac massage was begun. Epinephrine and sodium bicarbonate were injected into the heart. Rectal temperature was 108°F, so the lower body was packed in ice.

Serum and blood biochemical values were: glucose 356 mg%, urea nitrogen 21 mg%, uric acid 12.4 mg%, bilirubin 22 mg%, sodium 166 mEq/L, potassium 9.8 mEq/L, calcium 9.1 mg%, phosphorus 18.4 mg%, magnesium 2.2 mg%, creatinine 2.3 mg%, CK 420 IU, GOT 79 IU, LDH 325 IU, Paco<sub>2</sub> 53 mm Hg, pH 7.32, and base excess -4 mEq/L. Because resuscitative efforts were of no avail the patient was declared dead at 1230 hours.

*April 1975.* At age 14 years, E.B. Jr, the proband's paternal step-uncle, a muscular teenager, was admitted to our institution for a skeletal muscle biopsy for diagnosis of MH and repair of a left direct inguinal hernia. History and physical examination were normal except for the hernia and a markedly hyperactive personality; serum CK was 35 IU.

The anesthetic technique was as described for the patient's nephew, J.B. Both anesthesia and recovery were uneventful. The CHC test was borderline normal (CSC 4.45 mM, CSC-H 1.05 mM, and halothane contracture 0.00 gm).

*November 7, 1976.* The maternal half-uncle of the proband, J.C., was admitted to our institution for



investigation of MH and a right ureteral lithotomy. Apart from symptoms and signs referable to the kidney stone, history and physical examination were normal. The admitting serum CK was 49 IU. The CHC test was negative for MH; CSC 9.6 mM, CSC-H 1.44 mM, and halothane contracture 0.0 gm.

## Discussion

In the above family, multiple reactions occurred—several clearly induced by anesthetic agents (as in the second reaction experienced by the proband, C.B., and the fatal crisis suffered by her second cousin once removed, B.T. For several other reactions, stress—either before or after anesthetic-related crises may have played a contributory role or even a definitive role. For C.B., stress may even have helped trigger her first reaction because she had been noted to be extremely apprehensive during the last hours preceding induction. Similar observations of preanesthetic apprehension have been recorded by other workers (6-9). The postanesthetic reactions sustained by the proband's brother, J.B., may well have been entirely triggered by the stress of shivering induced by external cooling. Two reactions with fatal outcomes were totally unrelated to anesthesia. Thus the final fatal crisis suffered by C.B. appears to have been initiated by a combination of infection and stress, whereas in the reaction that killed her brother, J.B., emotional stress, cocaine and/or ethanol appear to have been responsible.

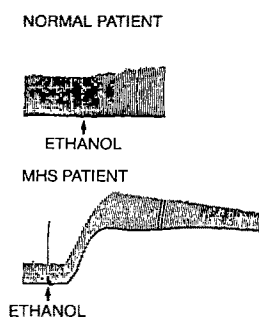
Preoperative stress or its lack may help to explain why a patient may not develop a MH crisis until after having had one or more previous normal anesthetics. The early uneventful anesthetics that preceded the MH reactions suffered by several members of this family may not have been associated with preanesthetic nervousness, whereas the final anesthetics may well have been preceded by apprehension. Of course many other factors may also be responsible for the phenomenon of several normal anesthetics preceding an MH reaction, for example, severity of the defect; type of anesthetics used; duration of anesthesia; level of exercise and/or muscle trauma before anesthesia; preoperative elevated serum calcium level or infection; and probably other as yet undefined factors.

Stress—probably pain—, physical stimulation, fear and/or shivering (induced by a too low setting of the K thermia machine) may well have been mainly or entirely responsible for the mild pyrexia episode that developed in J.B., after apparently safe anesthetics ( $N_2O$ , Innovar and diazepam). Similar postnarcotic and tranquillizer reactions have previously been re-

ported by Grinberg et al. (10) and by Lerman and Relton (11). Stress may also partly help explain why MH reactions, clearly initiated by potent inhalation anesthetics and/or skeletal muscle relaxants, tend to recrudescence for some considerable time in the PAR and/or intensive care unit.

For J.B., the roles of cocaine, ethanol, and emotional excitement in inducing his final fatal reaction are unclear. It could be that the three together each played a contributory role. On the other hand it might have been that one alone was responsible for the crisis and its fatal outcome. An MH crisis triggered by cocaine alone has never been reported. Furthermore, we have, without serious ill effects, used a 5% cocaine spray on the vocal cords during induction of anesthesia in more than 3000 MHS patients. The reaction that occurred in J.B. developed 3 hours after spraying the cords with cocaine and, therefore, was probably not secondary to use of this drug. On the other hand, lethal fever has been blamed for sudden death in individuals addicted to cocaine (12). Cocaine appears to elevate body temperature by potentiating the responses of sympathetically innervated organs, increasing muscle activity, and by stimulating the central temperature regulating center (12). The amount of cocaine absorbed into the blood stream after spraying of the vocal cords with cocaine spray is minute compared to that found in the blood of JB at postmortem examination. Such small amounts appear to be safe for analgesia of the vocal cords in MHS patients. Large amounts, however, may not be safe for these patients. It should be noted, however, that the postmortem levels of cocaine in the urine and stomach, and of its metabolite benzylcaine in the urine of JB were fairly modest, although undoubtedly considerably higher than those observed after spraying the vocal cords with 5% cocaine.

J.B. had a history of prior excessive use of ethanol which had on at least one occasion required a visit to a hospital emergency room. This abuse, however, had not previously resulted in pyrexia or other signs of MH. Nevertheless, it is known that in patients with severe MH whose skeletal muscles develop contractures in the presence of halothane alone, ethanol alone also causes contractures that closely resemble those induced by halothane (Fig. 2). Such ethanol-induced contractures are never observed in normal skeletal muscle fascicles. Additionally, J.B. Peter (personal communication) has described multiple deaths in a family after ingestion of small amount of ethyl alcohol. We observed a similar family in the late 1960s. The proband, a 16-year-old boy, died shortly after drinking his second glass of alcohol. His



**Figure 2.** Effect of ethanol on resting tensions on normal and MHS skeletal muscle fascicles. Muscle obtained from an individual with no history of MH in himself or his relatives and with a caffeine halothane contracture test in the normal range (with CSC > 4.1 mM and CSC-H > 1.05 mM) developed no contracture in the presence of 0.4 M ethanol. On the other hand, muscle obtained from a patient who had an MH reaction and a caffeine halothane contracture test in the MH range (CSC < 4.1 mM and CSC-H < 1.05 mM) developed a marked and sustained contracture in the presence of 0.02 M ethanol.

sister was, therefore, investigated at our institution. As part of this investigation she was given 2 ounces of gin in two divided doses to drink while her ECG and temperature were being monitored. After the second ounce she developed fever, chest pain, and signs of a myocardial infarct on the ECG. She spent 11 days in the coronary care unit. This case occurred before skeletal muscle biopsies for MH were being done, so the relation between MH and ethanol-induced crises has never been proven. Their similarity to anesthetic-induced MH is, however, sufficiently great that their identity cannot be ruled out.

J.B. was said to be extremely excited emotionally during the course of the evening's festivities. The role of this type of stress in inducing nonanaesthetic related human MH reactions has remained obscure and controversial. However, for many years emotional stress has been known to trigger MH crises in pigs (13-26). Recently a few reactions have occurred in human MHS patients that appear to have been caused at least in part by emotional stress (9,27-29). For example, Gronert et al. (29) in 1980 described a 42-year-old man who repeatedly developed episodes of fever, diaphoresis, malaise, fatigue, muscle pain, and weakness. On muscle biopsy the CHC test was positive for MH. Oral dantrolene sodium therapy provided prompt remission of symptoms and signs. In our laboratory we have investigated a patient with similar clinical picture and CHC test results. His symptoms and signs disappeared after initiation of oral dantrolene therapy. The repeated reactions in our patient—a middle-aged man who was the owner of a sizable business concern—occurred always at times when he was enduring great mental stress at work. Wingard (9,30,31) has described a family in

which 11 members had anesthetic-induced reactions while another 12 had stress-induced MH reactions. In one of the latter, a movie film documenting the muscle spasms was obtained.

The final reaction that terminated the life of C.B. appears to have been initiated by a flu-like illness. Whether the sudden rise in the temperature to 108°F accompanied by rigidity and cyanosis was due solely to an influenzal virus, or at least in part to an MH reaction triggered by either the early low-grade viral fever or by the Vick's Vapo Rub cannot be ascertained. We have, however, observed on a number of occasions that in MHS patients, fevers during apparently benign respiratory infections become much higher than expected. It may be, therefore, that fever itself may be able to kindle a MH crisis. Such MH reactions may occur not only secondary to infections, but also secondary to strenuous exercise in hot weather as demonstrated by Denborough (32). Additionally, it should be noted that Vicks Vapo Rub contains camphor 5%, eucalyptus 1%, cedar of oil compound 0.5%, nutmeg oil 0.5%, menthol 2.6%, thymol 0.8%, and spirits of turpentine 4.5%. Both menthol and thymol are alcohols and we have noted that thymol causes contractures in MHS muscle that resemble halothane-induced contractures.

## Conclusions

We have described a MH family in which reactions appear to have been triggered by a variety of factors—anesthetics (halothane, cyclopropane), succinylcholine, and perhaps stress (emotional excitement and infection) and abuse of drugs (cocaine and ethanol). In several reactions more than one factor was present. Which of these played the most major role in initiating and sustaining each of the reactions is not clear, but it is evident that these various triggers (particularly in combination) must be avoided by MHS individuals. Until the relative roles played by these various factors in triggering MH crises are better understood, those at risk for MH should be advised of the possibility that stress, alcohol, and cocaine, particularly in combination, may be capable of triggering MH reactions. This advice should especially be given to members of those families in which one or more reactions triggered by such factors have already occurred.

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## Massive Pulmonary Thromboembolism during Liver Transplantation

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**Key Words:** EMBOLISM—Thromboembolism.  
LIVER—Transplantation.

Pulmonary embolism occurs rarely during surgery, including liver transplantation, although posttransplantation pulmonary embolism has been reported (1-7). Usually, pulmonary embolism occurs in patients without liver disease. It would seem unlikely to occur in patients undergoing liver transplantation, who have deficient levels of coagulation factors and low platelet counts. We present a case of fatal massive pulmonary embolus in a patient undergoing liver transplantation. No previous cases have been reported in the literature.

### Case Report

A 30-year-old, 53-kg woman was transferred to our hospital 4 days after the onset of acute fulminant hepatitis. She was somnolent and unresponsive. Past medical history was unremarkable except for possible intravenous drug abuse. Physical examination revealed a comatose patient on mechanical ventilation. Blood pressure was 150/80 mm Hg; the heart rate was regular at 60 beats/min. Other findings included jaundice and absent pupillary responses.

Coagulation studies showed prothrombin time, 45 seconds (control, 25 seconds); activated partial thromboplastin time, 64 seconds (control, 25 seconds); and platelet count, 89,000/mm<sup>3</sup>. Chest radiogram, ECG, and other laboratory data were within normal limits. Serology studies were positive for hepatitis B surface antigen, antibody, and core anti-

gen, and for hepatitis A antibody. A computed tomogram of the head showed small ventricles suggestive of diffuse mild cerebral edema. The patient was receiving fresh frozen plasma at 800 ml/hr and platelets, 10 units per infusion, as indicated by thrombelastographic monitoring. Preoperative medications included lactulose and dexamethasone. After 1 day of hospitalization, the patient's condition did not improve, and a liver transplantation was scheduled.

Before the induction of anesthesia, two 8.5F catheters, a right radial artery catheter and a right internal jugular pulmonary artery catheter, were placed. Intraoperative monitoring included ECG, blood pressure, central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), and mass spectrometry. Coagulation was monitored by coagulation profile and thrombelastography (TEG).

Anesthesia, induced with lorazepam 2 mg and fentanyl 0.25 mg and followed by pancuronium 4 mg, was maintained with isoflurane and intermittent administration of pancuronium and fentanyl. Physiologic variables measured after the induction of anesthesia were within normal limits.

The dissection and isolation of the diseased liver were uneventful, and vital signs remained stable. By the time of removal of the diseased liver, the patient had received five units of packed red blood cells, five units of fresh frozen plasma, and ten units of platelets. Prothrombin time and activated partial thromboplastin time were prolonged: 45 seconds and 60.4 seconds, respectively. Platelet count was 187,000/mm<sup>3</sup>. Fibrinogen level was 280 mg/dl, and fibrin degradation products were negative. Blood coagulability was monitored by TEG, as described by Kang et al. (8).

The venovenous bypass system consisted of inflow of blood from the left femoral and portal veins, a Biomedicus centrifugal pump, and outflow to the left axillary vein. The inflow and outflow tubings

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were heparin-coated (Gott Aneurysm shunt). The system was primed with Plasmalyte solution before institution of bypass. The bypass flow was maintained at 3 L/min, and vital signs did not change significantly: blood pressure was 130/80 mm Hg, heart rate 90 beats/min, CVP 8 mm Hg, PAP 26/14 mm Hg. Hepatitis B immune globulin (100 ml) was infused intravenously in an attempt to eradicate the hepatitis virus. After 10 minutes of bypass, acute hemodynamic changes occurred while the suprahepatic inferior vena caval anastomosis was being performed. The blood pressure decreased to 60/40 mm Hg and heart rate to 30 beats/min, PAP increased to 100/40 mm Hg, and CVP to 50 mm Hg, while PCWP decreased to 2 mm Hg. The end-tidal CO<sub>2</sub> measured by mass spectrometry, decreased to 0.92%. Bilateral breath sounds were equal. An air embolus was suspected, but two aspirations of the central venous and pulmonary artery catheters revealed no air. Acute pulmonary thromboembolism was then diagnosed. Resuscitative measures were carried out immediately using atropine 1 mg, epinephrine 1 mg, CaCl<sub>2</sub> 1 g, and NaHCO<sub>3</sub> 50 mEq. The vital signs deteriorated rapidly. Closed- and then open-chest cardiac massage was performed but did not improve the patient's hemodynamics, and the patient died intraoperatively.

Postmortem examination revealed 150 ml of soft thrombus in the right atrium, right ventricle, pulmonary arterial trunk, and both proximal pulmonary arteries.

## Discussion

Intraoperative pulmonary embolism is uncommon, but its acute effects on the cardiopulmonary system can be major. The severity of these effects is determined by the extent of the embolic occlusion and the hemodynamic condition of the patient before it occurs. The hemodynamic and pulmonary changes have been described by McIntyre and Sasahara (9). In a healthy subject, the right ventricle can function without signs of pulmonary hypertension if the pulmonary vascular bed is occluded <50% (10). Beyond 50% occlusion of the pulmonary vascular bed, acute cor pulmonale occurs, with a reduction in forward blood flow. In a patient with impaired right ventricular function, cor pulmonale may develop with less obstruction. Our patient had almost total obstruction of the pulmonary artery, evidenced by very low PCWP, sinusoid radial arterial waveform, and unsuccessful attempts at resuscitation.

In our patient, pulmonary air embolus was initially suspected. Air embolism has been reported to occur

in patients with liver disease, owing to right-to-left shunting, and during major vascular surgery such as liver surgery. Failure to aspirate air from central venous catheters made the diagnosis of air embolism less likely and thromboembolism far more likely.

The treatment of thromboembolism consists of halting the embolic process, restoring the pulmonary vascular bed to as normal a state as possible by using inotropes to increase forward flow, and providing thrombolytic therapy with streptokinase, urokinase, and heparin. Pulmonary embolectomy, even when experienced personnel and equipment are available, is now rarely performed (10,11). The mortality rate among patients with massive pulmonary embolism is about 75% in the first hour (5). In this patient emergency pulmonary embolectomy might have increased blood flow to the left side of the heart, but it was not attempted because of the high mortality associated with pulmonary embolism with or without pulmonary embolectomy.

The cause of pulmonary embolism in this patient remains uncertain. In patients with end-stage liver disease, decreased levels of coagulation factors and platelets are common owing to impaired hepatic synthetic function and to splenic pooling, which removes circulating platelets. With these conditions, thrombus formation in our patient was unlikely. On the other hand, disseminated intravascular coagulation (DIC) is reported to occur in patients with liver disease because of a rapid turnover of fibrinogen, fibrinolysis, and generalized thrombus formation in the systemic circulation. All these factors may have caused thromboembolism in this patient. Autopsy findings in cirrhotic patients have shown a very high incidence of thrombosis of the major vessels, including the portal vein and esophageal varices. Fibrin deposits in the capillaries, a common feature in DIC, are not found in the cirrhotic patients (9,12). Although Mant and King (13), in a study of severe, acute DIC, concluded that large-vessel thrombosis (predominantly venous) is relatively common in association with DIC, heparin is seldom used in the medical management of DIC. Our patient had a relatively short course of hepatic dysfunction, but thrombus formation in the portal and systemic venous system is possible. If the patient had preexisting thrombus formation in major vessels, it could have migrated to the pulmonary artery via the venovenous bypass system, which has little resistance (14).

Our patient received hyperimmune globulin intraoperatively before the embolic episode. Antigen-antibody complex formed as a result of this therapy could have activated the intrinsic pathway of the coagulation cascade (15). Whether the formation of

such complexes between circulating viral antigens and administered immunoglobulins could have played a role in the formation of thrombus is uncertain. Epsilon-aminocaproic acid has been shown to treat fibrinolysis during liver transplantation when used in small doses. Large doses, however, can cause thrombus formation (16). No epsilon-aminocaproic acid was given to this patient.

Overzealous correction of coagulopathies could have contributed to thrombus formation. However, the coagulation profile and thrombelastogram showed poor coagulation, possibly from deficient platelets and dilutional coagulopathy. The thromboembolism could have been caused by acceleration of coagulation by the contact of blood with the venovenous bypass system. Although the centrifugal pump was not heparinized, the tubing was heparin-coated. The system has been used experimentally in healthy animals at our institution, and thrombus formation was not observed, even in low-flow states ( $<1$  L/min). Heparin may be given before instituting bypass to prevent thrombus formation. However, our early experience showed us that systemic heparinization caused devastating coagulopathy and uncontrollable bleeding. Further study is needed to assess whether or not the use of heparin to prime the system would prevent thromboembolic phenomena.

In summary, we have described a case of fatal pulmonary thromboembolism in a patient undergoing liver transplantation. Its possible causes include DIC, overzealous treatment of DIC, hyperimmune globulin and viral antigen complex formation, and lack of heparinization in the centrifugal pump used for venovenous bypass.

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## Delayed Postoperative Respiratory Depression Associated with Oxymorphone

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**Key Words:** ANALGESICS—oxymorphone.

Oxymorphone (Numorphan), a potent, semisynthetic opioid analgesic with pure agonist properties, is being used with increasing frequency as the narcotic base of balanced anesthesia (1,2). Oxymorphone analgesia is associated with respiratory depression, but delayed postoperative respiratory depression has not been reported. A case of delayed postoperative respiratory depression after anesthesia with oxymorphone as its main component is described.

### Case Report

A 51-year-old, 75-kg woman with ovarian adenocarcinoma was scheduled for a "second-look" laparotomy. She had undergone a radical hysterectomy as well as other surgical procedures in the past, without problems. Radiation and chemotherapy were administered 1 year before admission without sequelae. She was neither cachectic nor dehydrated.

Premedication was administered with triazolam (Halcion) 0.25 mg. In addition, IV midazolam was administered (2 mg preoperatively and 1 mg intraoperatively). The dosage of oxymorphone (0.1 mg/kg) was calculated on the basis of recent reports describing the use of oxymorphone as the primary component of balanced anesthesia for surgical procedures of moderate to long duration (1,2). Oxymorphone 7.5 mg was administered IV in 1.5-mg increments over 10 minutes. It has been suggested that the potency of oxymorphone ranges between seven and ten times that of morphine, so that our calculated dose of oxymorphone would have been roughly equivalent to the administration of 50 to 75 mg morphine sulfate

for this 75-kg patient. The patient demonstrated mild euphoria, respiratory rate decreased to 12 breaths/min, but there was no loss of consciousness, chest wall rigidity, or alterations in blood pressure or pulse rate. In the operating room, the anesthetic induction was completed after the administration of curare 3 mg, with thiopental 175 mg and lidocaine 100 mg, followed by succinylcholine 100 mg. The trachea was intubated, and anesthesia was maintained with 70% nitrous oxide in oxygen. Atracurium was administered in doses sufficient to preserve two twitches on the train-of-four. Pulse, blood pressure, and temperature remained stable throughout, and at the end of the 3-hour and 30-min procedure muscle relaxation was reversed with edrophonium 60 mg and atropine 0.4 mg. One to 2 minutes after 100% oxygen was administered the patient could follow simple commands (sustained head lift, hand grasp, vital capacity), and her trachea was extubated.

On admission to the postanesthesia care unit (PACU), nursing records indicate that the patient was "extremely comfortable; respirations: deep; color: pink; temperature 36.5°C, blood pressure 120/80 mm Hg, pulse rate 85 beats/min, respiratory rate 16 breaths/min." Vital signs 55 minutes later on discharge from the PACU and return to the patient's room were unchanged except for an increase in respiratory rate to 22 breaths/min. The patient was coherent, moved herself to her bed, and declined pain medications. Nursing notes indicate that the "patient was talking and laughing and excited about outcome of surgery." Thirty minutes later the nursing staff was informed by her husband that she had become gradually less responsive. The patient was unrousable, cyanotic, and respirations were absent. A code signifying cardiorespiratory arrest was announced, although pulse and blood pressure were 60 beats/min and 120/80 mm Hg, respectively. Intubation of the trachea was delayed to observe the response to a trial of naloxone. She became responsive within 30-60 seconds of the IV administration of 0.4 mg naloxone, and thereafter had an uneventful re-

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covery. A venous blood sample obtained before treatment with naloxone had a pH of 7.11,  $Pv_{CO_2}$  of 79 mm Hg, and  $Pv_{O_2}$  of 26 mm Hg. Ten minutes after treatment, an arterial blood sample obtained while the patient breathed 40% oxygen showed a pH of 7.33,  $Paco_2$  of 38 mm Hg, and  $Pao_2$  of 185 mm Hg.

## Discussion

The duration of analgesic action of oxymorphone ranges from 4 to 6 hours. This report documents profound respiratory depression occurring 5½ hours after drug administration, and following a 1 hour and 35 minute period during which the patient was breathing adequately.

Predisposing factors that might increase sensitivity to respiratory depression were sought. There were no abnormalities in hepatic or renal function, temperature was normal, and no additional drugs had been administered inadvertently. We believe that the patient's apparent full recovery from anesthesia was related to continuous environmental stimulation during one-on-one postanesthesia nursing care. The possibility that latent peak plasma concentrations may occur with oxymorphone, as observed with fentanyl (3), deserves consideration.

We are not aware of any report of profound respiratory depression occurring so long after the administration of oxymorphone after apparent full recovery. We recommend careful observation for a prolonged period after the administration of large doses of oxymorphone. Based on other reports of prolonged narcosis in elderly patients receiving morphine (4), meperidine (5), and fentanyl (6), additional caution should be exercised in the aged patient.

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## Sufentanil-Midazolam Anesthesia in Malignant Hyperthermia

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**Key Words:** HYPERTHERMIA—malignant.  
ANALGESICS—sufentanil.  
HYPNOTICS, BENZODIAZEPINES—midazolam.

Use of narcotics and benzodiazepines in patients with malignant hyperthermia (MH) is generally considered safe (1). Nevertheless, new drugs of either type can be considered safe only after undergoing testing in malignant hyperthermia-susceptible (MHS) animals and/or after uneventful clinical use in known MHS patients. There are no reports of the use of sufentanil and/or midazolam in such settings and the cases described herein are believed to be the first description of the safe use of these agents in three MHS patients.

### Report of Three Cases

#### Case 1

The patient was a 13-year-old, 72-kg male with a history of histopathologically proven Duchenne's muscular dystrophy who was scheduled for posterior spine fusion with rod placement for progressive kyphosis. A prior anesthetic for eye muscle surgery at 4 years of age triggered an episode of successfully treated MH, later proven by halothane-caffeine contraction testing of vastus lateralis muscle. Preoperative evaluation revealed a moderately obese young male with thoracolumbar kyphosis, upper and lower limb contractures and proximal muscle weakness. An echocardiogram demonstrated dilation and impaired contractility of the left ventricle consistent with a cardiomyopathy. Pulmonary function tests demonstrated a moderately severe restrictive defect with 60% of predicted vital capacity and FEV<sub>1</sub>/FVC equaling 0.92. The patient took no medications preoperatively.

Preanesthetic medication consisted of 10 mg diazepam orally. Dantrolene (2.5 mg/kg) and cefazolin were administered IV in the anesthesia preparation area. Twenty minutes later anesthesia was induced with 100 mg thiopental, 100  $\mu$ g sufentanil, and 5 mg midazolam IV. Muscle relaxation was achieved with 6 mg vecuronium, which completely ablated all cutaneous nerve stimulator response. After tracheal intubation, anesthesia was maintained with 50% nitrous oxide and continuous infusions of 0.5  $\mu$ g·kg<sup>-1</sup>·hr<sup>-1</sup> sufentanil and 0.1 mg·kg<sup>-1</sup>·hr<sup>-1</sup> midazolam. Ventilation was controlled using a nonrebreathing system (Siemen's Elema Servo Ventilator 900C). Monitoring included continuous ECG, intraarterial and central venous pressure, central venous oxygen saturation, pulse oximetry, capnography, rectal temperature and somatosensory evoked potentials using the posterior tibial nerves. Neuromuscular blockade was monitored (with a peripheral nerve stimulator applied over the ulnar nerve). Additional increments of vecuronium (0.5 mg IV  $\times$  2) were administered over the ensuing 6.5 hours to maintain blockade of the first three of a train-of-four twitches. Three hours elapsed from the induction dose of vecuronium until any twitch response occurred. The intraoperative course was uneventful (arterial blood pressure ranged between 90–110/60–70 mm Hg, temperature between 35.9 to 36.5°C, heart rate 80–90 beats/min without arrhythmias, end-tidal CO<sub>2</sub> 26–34 mm Hg, base deficit 0 to –2 mEq/L, and no venous oxygen desaturation throughout). Residual muscle relaxant was reversed with 20 mg pyridostigmine and 0.4 mg glycopyrrolate and the patient extubated awake and pain-free 10 minutes after arrival in the recovery room.

The patient's postoperative course was similarly uneventful, except for two elevations of temperature to 39.1°C, which were unaccompanied by any other changes in vital signs, metabolic or respiratory acidosis, or venous desaturation. These temperature elevations were believed to be secondary to atelectasis that was roentgenographically documented. Twenty-four hours postoperatively serum creatine phospho-

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kinase (CPK) was 826 IU/L (nl, 25-145), an increase above preoperative levels (468 IU/L) attributed to surgical muscle trauma. No dantrolene was administered in the postoperative period and the patient was discharged 10 days later.

### Case 2

The patient was a muscular 17-year-old, 76-kg male with the diagnosis of hereditary spherocytosis who was brought to the operating room for splenectomy. At the age of 9 years, severe masseter spasm and tachycardia during induction of anesthesia for tonsillectomy prompted cancellation of surgery. Subsequent halothane-caffeine muscle contraction testing was positive for MHS. Preoperative medications included hydrocortisone, pneumococcal vaccine, and cefazolin. Preoperative laboratory tests revealed a normal serum CPK level and a hemoglobin level of 9.6 g/dl. After oral premedication with 10 mg diazepam, an intravenous catheter was inserted and dantrolene (2.5 mg/kg) was administered. Induction of anesthesia and tracheal intubation were achieved with 125  $\mu$ g sufentanil, 7 mg midazolam, and 6 mg vecuronium. Anesthesia was maintained for 2.5 hours with 50% nitrous oxide and continuous infusions of 0.5  $\mu$ g·kg<sup>-1</sup>·hr<sup>-1</sup> sufentanil and 0.1 mg·kg<sup>-1</sup>·hr<sup>-1</sup> midazolam. Ventilation was controlled with a nonbreathing system (Siemen's Elema, Servo ventilator 900C).

Monitoring included continuous intraarterial, central venous and pulmonary artery pressures, ECG, rectal and pulmonary artery temperature, pulse oximetry, oximetric mixed venous oxygen saturation, capnography, and neuromuscular blockade monitoring. Intraoperatively, systemic blood pressure ranged between 100-130/60-76 mm Hg, bladder temperature 36.4-37.2°C, heart rate 90-110 beats/min without arrhythmias, end-tidal CO<sub>2</sub> 28-34 mm Hg, base deficit 0 to -2 mEq/L, and mixed venous oxygen saturation 58-71% throughout. No additional doses of vecuronium were needed to maintain blockade of three of the train-of-four twitches for 3 hours, at which time residual neuromuscular blockade was reversed with 5 mg neostigmine and 0.6 mg glycopyrrolate. The patient was extubated, awake, and pain-free in the operating room. The postoperative course was uneventful except for temperature elevations (maximum of 37.9°C) beginning 32 hours after surgery that were unaccompanied by any other signs of MH. The fever decreased after incentive spirometry was begun. Serum CPK levels were within the range of normal laboratory values 8, 24, and 48 hours postoperatively.

### Case 3

The patient was a 52-year-old, 98-kg male undergoing resection of an abdominal aortic aneurysm and renal artery revascularization. A family history of MHS (two nephews) prompted preoperative halothane-caffeine muscle contraction testing that was strongly positive. His only prior exposure to anesthesia was for a toe amputation performed under spinal anesthesia. Past history was significant for an old myocardial infarction, chronic atrial fibrillation, and mild obstructive lung disease. The patient was receiving digoxin for control of heart rate. Preoperative laboratory evaluation demonstrated mild polycythemia (hemoglobin 15.8 g/dl) and a normal serum CPK level. After oral premedication with 15 mg diazepam, an IV infusion of 2.5 mg/kg dantrolene was administered. Induction of anesthesia and tracheal intubation were achieved with 175  $\mu$ g sufentanil, 9 mg midazolam, and 10 mg vecuronium, which completely ablated all twitches from a cutaneous nerve stimulator. Anesthesia was maintained for 5 hours with 50% nitrous oxide and continuous infusions of 0.5  $\mu$ g·kg<sup>-1</sup>·hr<sup>-1</sup> sufentanil and 0.1 mg·kg<sup>-1</sup>·hr<sup>-1</sup> midazolam. Ventilation was controlled using a nonbreathing system as in the first two cases.

Monitoring included continuous intraarterial, central venous and pulmonary artery pressures, ECG, rectal and pulmonary artery temperatures, pulse oximetry, oximetric mixed venous oxygen saturation, capnography, and neuromuscular blockade monitoring. There was complete abolition of twitches for 3 hours and subsequently 1 mg of vecuronium produced blockade of three of the train-of-four twitches for an additional 2.5 hours. Intraoperatively systemic blood pressure ranged between 150-110/84-56 mm Hg, core temperature 36.3-36.6°C, heart rate 56-80 beats/min without any change in rhythm, pulmonary capillary wedge pressure 9-16 mm Hg, cardiac output 4.2-5.2/L min, end-tidal CO<sub>2</sub> 29-36 mm Hg, base deficit 0 to -2 mEq/L, and mixed venous oxygen saturation 66-68% throughout. Intravenous nitroglycerin was used during aortic cross-clamping and was not needed after revascularization. No bicarbonate was administered at any time. Abolition of three of the train-of-four twitches was present at the end of surgery. Residual muscle relaxant was reversed with 20 mg pyridostigmine and 0.6 mg glycopyrrolate, and after discontinuing N<sub>2</sub>O, the patient was awake, comfortable, and extubated 3 hours later in the intensive care unit.

The patient's postoperative course was uneventful except for a mild increase in serum creatinine to 1.6 mg/dl from 1.3 mg/dl. He had no fever, changes in

vital signs, acidemia, or venous desaturation. Twenty-four hours after surgery the serum CPK level was normal. No dantrolene was administered after the initial preoperative dose.

## Discussion

The effects of midazolam on directly stimulated muscle biopsies from control and malignant hyperthermia-positive patients has been studied (2). There appear to be no detectable effects on muscle contraction in MHS or control preparations and no interactions between midazolam and either halothane or caffeine on the resting tension of directly stimulated muscle. Nonetheless, clinical trials remain the only means of determining the potential of a drug to produce MH in humans with known MHS. The manufacturers of midazolam and sufentanil were unable to provide information on the use of either drug in MHS patients. In addition, there are no studies reporting the use of sufentanil in MHS animals. We believe these cases are the first reports of safe clinical use of sufentanil and midazolam in patients susceptible to malignant hyperthermia.

The anesthetic techniques employed in these cases involved the use of a "loading" dose of each agent and then continuous infusions to avoid fluctuations in serum drug levels, to minimize the total administered dose and to provide a more stable level of neuroleptanesthesia. Avoidance of stimulation during light anesthesia is important in avoidance of triggering of MH responses (1). This technique also allows for smooth, rapid awakening with resumption of spontaneous ventilation while providing initial postoperative analgesia. We have successfully employed this technique in a variety of patients and surgical procedures with success and this prompted its trial in these MHS patients. Additionally, the pharmacokinetic profile of these three agents provides the clinician with a broader choice for MH-susceptible patients, especially during procedures of short-to-moderate duration.

Although it has been shown that vecuronium is not a trigger of MH in susceptible pigs (3), its use in patients with biopsy-proven MHS has not been reported. We used it with care because of the reports of prolonged vecuronium neuromuscular blockade in a patient receiving dantrolene (4) (because of a family history of MH). We similarly noted an abnormal prolongation of clinical relaxation caused by vecuronium after pretreatment with dantrolene, especially in the first patient who also had proximal muscle weakness secondary to Duchenne's muscular dystro-

phy (complete neuromuscular blockade lasting 3 hours after 0.08 mg/kg vecuronium). The second and third patients also had an unusually long duration of action of vecuronium despite normal temperature, acid-base, and electrolyte status, and lack of exposure to aminoglycosides. Dantrolene in doses <2 mg/kg has been shown to cause a dose-dependent depression of twitch tension in humans (5). Dantrolene mainly acts to interfere with sarcoplasmic calcium transport, but also may affect release of calcium from storage sites in the cholinergic nerve terminal with a resultant decrease in transmitter mobilization at the neuromuscular junction (6). The latter effect may be responsible for the prolonged muscle paralysis from vecuronium after dantrolene pretreatment. It appears that vecuronium should be used with careful monitoring of neuromuscular function whenever dantrolene is administered, especially in the presence of myopathies not due to MH alone.

Additionally, the first case is another demonstration that patients with Duchenne's muscular dystrophy are susceptible to malignant hyperthermia (7), and that it is important to maintain a high degree of suspicion of the increased potential for MH in patients with any signs of muscular dystrophy who require anesthesia.

Anesthesia-induced malignant hyperthermia can be difficult to diagnose clinically because the full syndrome is not always manifested. Based on our observations of no pyrexia, muscle rigidity, acidosis,  $Paco_2$  elevations, venous oxygen desaturation, lack of arrhythmias, or unexplained postoperative serum creatine phosphokinase elevations, we believe this suggests that midazolam, sufentanil, as well as vecuronium can be safely used in known MH-susceptible patients. Because malignant hyperthermia-susceptible swine are much more sensitive to triggers than are humans, controlled testing in MHS swine is needed to further confirm the safety of these useful drugs in MHS patients.

In summary, this is the first report of the safe use of sufentanil and midazolam in three patients with biopsy-documented malignant hyperthermia syndrome. We believe the use of loading doses of each agent followed by continuous infusions is a technique that provides the clinician another choice for short-to-intermediate length procedures requiring general anesthesia in MHS patients.

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## Caudal Epidural Morphine for Post-Thoracotomy Pain

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**Key Words:** ANESTHETIC TECHNIQUES, EPIDURAL—morphine. PAIN—postoperative. ANALGESICS—morphine.

Epidural opioids, injected at either a thoracic or lumbar level, provide long lasting pain relief after thoracic operations (1-5). We report the successful use of caudal morphine for analgesia after a pulmonary resection in a patient who had a recent lumbar laminectomy.

### Case Report

A 58-year-old man with chronic low back pain underwent lumbar laminectomy at the L3-4 level. On the morning of surgery, a chest x-ray revealed a suspicious lesion in his left upper lobe. Seven days after the laminectomy, he returned to the operating room for a thoracotomy.

Past medical history was significant for acromegaly treated by transsphenoidal hypophysectomy 6 years before the current admission. Physical examination revealed a 91-kg, 180-cm male with acromegalic facial features. Blood pressure was 110/66 mm Hg, heart rate 54 beats/min, and respiratory rate 14 breaths/min. The chest was clear to auscultation.

The patient was unpremedicated. In the operating room intravenous and radial artery catheters were inserted. While in the prone position, an epidural catheter was advanced 3 cm past the end of a needle inserted into the caudal canal. After the catheter was taped to the skin, the patient returned to the supine position. A test dose of 4 ml of 1.5% lidocaine with 1/200,000 epinephrine was administered through the caudal catheter. The patient remained hemodynamically stable. Five minutes later an additional 1.5% lidocaine with 1/200,000 epinephrine to a total volume of 35 ml was injected through the catheter. After

10 minutes, decreased sensation to pinprick was apparent to a T6 dermatomal level bilaterally.

The patient was then given 100% oxygen for 2 minutes, followed by intravenous thiopental for induction of general anesthesia. Succinylcholine was given to facilitate intubation with a 41F polyvinyl chloride double-lumen endobronchial tube. General anesthesia was maintained with isoflurane (1%) and oxygen throughout the 150-minute procedure. The patient received small amounts of pancuronium for relaxation. Approximately 75 minutes after the initial caudal injection of lidocaine, a second injection of 35 ml of 1.5% lidocaine with 1/200,000 epinephrine was given to supplement the general anesthesia. Sixty minutes before the completion of surgery, 10 mg of preservative-free morphine sulfate in 20 ml of saline solution was injected through the caudal catheter. Fifteen minutes before the completion of surgery, 75  $\mu$ g of fentanyl in 20 ml of sterile saline was also injected through the caudal catheter.

The patient underwent a left upper lobectomy through a postero-lateral thoracotomy incision. At the completion of surgery, muscle paralysis was reversed with neostigmine and glycopyrrolate. The isoflurane was discontinued. The patient awoke pain-free and alert, and his trachea was extubated in the operating room. He was transferred to the intensive care unit in stable condition. There were no intraoperative surgical or anesthesia complications.

He first required supplementation of the caudal morphine with 10 mg of morphine in 20 ml of saline 6 hours after his initial intraoperative morphine. He was transferred to a surgical ward from the ICU on the first postoperative day with the caudal catheter in place.

Postoperative analgesia was provided with preservative-free morphine, 10 mg in 10-20 ml of saline through the caudal catheter given every 6-12 hours. He was quite comfortable with just this regimen. He was out of bed and ambulatory on the first postoperative day. He did not develop pruritis or urinary retention. The caudal catheter was removed on the third postoperative day. Afterward, pain control was

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achieved with oral analgesics (acetaminophen and codeine) every 3-6 hours as needed. He did not receive parenteral (IV or IM) opioids for postoperative analgesia at any time. The patient was discharged from the hospital of the sixth postoperative day in good condition.

Having undergone two major operations within 1 week, he was asked to compare the degree of pain relief after each. He felt that the analgesia from the caudal morphine after thoracotomy was markedly superior to the pain relief he experienced after laminectomy when he had been treated with IV and IM morphine.

## Discussion

The benefits of epidural opioids after thoracic surgery are well documented. Patients are comfortable, ambulate sooner, and have improved pulmonary function compared to patients treated conventionally with parenteral opioids (4). It is our usual practice to administer morphine or hydromorphone through a lumbar epidural catheter for all patients undergoing thoracotomy. In our clinical experience, either of these two agents, when given at the lumbar level, provide excellent analgesia after thoracotomy without exposing patients to the small but real risk of spinal cord damage from placement of a thoracic epidural catheter. We were unwilling to attempt to catheterize the lumbar epidural space in this patient because he had undergone lumbar laminectomy just 7 days earlier, and the patient would not allow us to place a thoracic epidural catheter either before or during surgery.

It is unclear whether the analgesia from epidural opioids is segmental in nature or whether rostral spread within CSF makes the actual level of injection unimportant. Therefore, we decided to try the caudal route. Although caudal opioids have been successfully used for anorectal and urogenital surgery (6), we are unaware of any reports of their use after thoracotomy in adults. Because we had no guidelines for the dose or volume of drugs needed, we arbitrarily used a 20-ml volume instead of the 10-15 ml we normally give at the lumbar level for post-thoracotomy analgesia. A larger amount of morphine (10 mg instead of 5-7.5 mg) was also used. Although some of the morphine solution probably leaked out of the epidural space at the site of the recent laminectomy, by using a relatively large dose of morphine and a large volume of solution, there was either increased spread of the drug in the CSF or up the epidural space itself. Leakage of drug from the epidural space may also account for the relatively shorter duration of

action we observed in our patient. In view of the relatively large doses of morphine used, higher than normal systemic levels from vascular absorption were probably present. However, it is unlikely that systemic levels were the main source of analgesia because the patient was more comfortable and more alert than he had been after surgery the previous week when he was treated with parenteral morphine alone.

Opioids with low lipid solubility, like morphine, diffuse readily in CSF and are effective for relief of post-thoracotomy pain when injected at the lumbar level (5). We therefore choose hydrophilic morphine rather than a more lipophilic agent such as hydromorphone because morphine was more likely to spread to higher cord levels (7). Pain relief was complete and the patient required no other pain medication while treated with caudal morphine. He experienced no evidence of respiratory depression or any of the minor side effects (pruritis, urinary retention, nausea, or sedation) that may be associated with epidural morphine.

In summary, although lumbar or thoracic epidural opioids are the usual choice for post-thoracotomy analgesia, we had a patient in whom we were unable to use either of these routes. He was given preservative-free morphine through a catheter placed in the caudal epidural space and experienced total relief of post-thoracotomy incisional pain without undesirable side effects. Caudal epidural opioids should be considered for postoperative analgesia after abdominal and/or thoracic surgery when the alternative lumbar or thoracic epidural routes cannot be used.

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## High Frequency Positive-Pressure Ventilation for Anterior Thoracic Spine Fusion after a Previous Pneumonectomy

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**Key Words:** VENTILATION—high frequency.  
SURGERY—orthopedic.

High frequency ventilation (HFV) has gained increasing utilization in both the operating room and the intensive care unit (1). Intraoperatively, HFV has facilitated lung resections, certain abdominal procedures, bronchial and laryngeal surgeries and, most recently, has been applied to extracorporeal shock wave lithotripsy (ESWL) (1-6). Three different gas delivery techniques have been grouped together under the heading of HFV. One of these three techniques, high frequency positive-pressure ventilation (HFPPV), may be carried out with a number of conventional ventilators utilizing respiratory frequencies of 60-120 breaths/min with tidal volumes of 1.5-3 ml/kg (1). Another high frequency jet ventilation (HFJV) delivers compressed gas through a small cannula placed in the respiratory tree at frequencies up to 600 breaths/min (1). The third technique, high frequency oscillation (HFO), uses frequencies up to 40 Hz (2400 cycles/min) with oscillation volumes from 1 ml/kg up to 3 ml/kg (1).

Each of the above techniques has advantages, applications, and limitations (5). Many studies have demonstrated adequate or improved respiratory gas exchange with the different modes of HFV (1-6). However, both HFJV and HFO may be difficult to use during anesthesia (3,7). HFPPV, utilizing a Siemens-Eléma anesthesia machine, has recently been used for ESWL and ventilating parameters for optimum carbon dioxide (CO<sub>2</sub>) elimination have been proposed (4). Tidal volumes of 1.5-3.0 ml/kg at rates of 100 breaths/min allow for CO<sub>2</sub> removal and the adminis-

tration of N<sub>2</sub>O, O<sub>2</sub> and a potent inhaled anesthetic (4).

We report a case in which HFPPV utilizing a Siemens-Eléma anesthesia machine was used for an anterior spine fusion through a thoracotomy in a patient with a previous contralateral pneumonectomy.

### Case Report

A 69-year-old man weighing 99 kg was scheduled for left thoracotomy and anterior spine fusion. Several years previously, the patient had a right pneumonectomy for adenocarcinoma of the lung. He remained asymptomatic until 4 months before admission, at which time he experienced right-sided chest wall pain and back pain. Radiographic studies indicated probable metastatic disease involving the right 8th rib and the T7-9 vertebral bodies. Conservative therapy having failed, it was proposed to relieve the patient's pain by performing posterior spine stabilization with Harrington rod insertion and a left thoracotomy with anterior spine fusion and rib resection.

Preoperative evaluation showed an obese, elderly male in no respiratory distress at rest, although mild exertion produced dyspnea. He reported no history of cardiovascular disease and his only medication was methadone. Physical examination was significant for the absence of breath sounds over the right chest and a normal neurologic examination. Pulmonary function studies showed a forced vital capacity (FVC) of 44% of predicted and a forced expired volume (FEV 1) of 51% predicted. Arterial blood gas (ABG) tensions measured while breathing room air were pH 7.44, Po<sub>2</sub> 81 mm Hg, Pco<sub>2</sub> 44 mm Hg. Chest x-ray showed an opacified right hemithorax.

After consultation with the surgical team it was apparent that considerable retraction of the remaining lung would be required to be able to perform the anterior spine fusion. In a patient with normal pul-

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Table 1. Hemodynamic and Respiratory Data

Time	Hemodynamic data					
	HR (beats/min)	Mean BP (mm Hg)	RAP (mm Hg)	Mean PAP (mm Hg)	PCWP (mm Hg)	CI (L·min·m <sup>2</sup> )
Postinduction	81	70	18	26	18	2.7
Prethoracotomy	92	79	19	30	23	3.2
Thoracotomy	78	88	13	26	16	2.8
Post-thoracotomy	78	92	9	22	12	2.9
8 hr Post-op	115	80	9	26	9	3.8

HR, Heart rate; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; PVR, pulmonary vascular resistance; ABG, arterial blood gas tensions; MVBG, mixed venous blood gas tensions;  $Q_p/Q_t$ , pulmonary shunt calculated; RR, respiratory rate; Exp TV, expired tidal volume; Paw, peak airway pressure.

monary anatomy and function, such a case could have been performed with a double-lumen endotracheal tube and one-lung ventilation. An anesthetic plan involving HFPPV was developed. After premedication with morphine, diazepam and glycopyrolate, a radial arterial catheter and pulmonary artery catheter were inserted. Anesthesia was induced with midazolam, fentanyl, and thiopental, orotracheal intubation with a 8.5-mm tube being facilitated with pancuronium bromide for muscle relaxation. Anesthesia was maintained with 1:1 ratio of O<sub>2</sub>/N<sub>2</sub>O with inspired isoflurane concentrations ranging from 0.25 to 0.75%. Supplemental dosages of fentanyl and pancuronium bromide were added as required. Monitoring included ECG (modified lead 2), somatosensory evoked potentials (SSEPs), mass spectrometry, pulse oximetry, and an end-tidal CO<sub>2</sub>.

The patient was ventilated utilizing a Siemens-Elema 900-D ventilator. Initially intermittent positive-pressure ventilation (IPPV) with a respiratory rate of 10 breaths/min and a tidal volume of 900 ml was used. Baseline hemodynamic and respiratory parameters were recorded after induction in the lateral decubitus position. Before the thoracotomy the ventilation was changed to HFPPV at a rate of 80 with a tidal volume of 250 ml (2.5 ml/kg) at an inspired to expired ratio of 1:2.5.

HFPPV was maintained throughout the thoracotomy and anterior spine fusion. Conventional IPPV was resumed at the time of chest closure. Hemodynamic and respiratory data, as well as blood gas tensions were recorded during each phase of the operation (Table 1).

During HFPPV there were small movements of the thorax and lung tissue; however, the operative field was noted to be free of intruding lung parenchyma. After the 7-hour procedure, muscle paralysis was reversed and the patient was extubated without difficulty. Postoperatively the patient had an uneventful recovery without pulmonary complications.

## Discussion

A patient scheduled for anterior thoracic spine fusion is presented in whom the complicating factor of a previous contralateral pneumonectomy was involved. Thoracotomies for anterior spine surgery require the anesthesiologist to maintain adequate respiratory gas exchange while optimizing surgical exposure. Lung retraction and compression, as well as mediastinal compression, may occur as surgical exposure is gained. One lung ventilation utilizing a double-lumen endotracheal tube has been employed in the past, but that option was impossible in our case because of the previous pneumonectomy.

HFPPV was one of few options available to our patient. If adequate gas exchange and hemodynamics could not be maintained by HFV, the only other techniques facilitating surgery would have been cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO). CPB would probably have increased the duration of the operation and the amount of blood loss and morbidity involved in the procedure.

HFV, either HFJV or HFPPV, has been applied successfully in thoracic surgery (2,3,8). Advantages over conventional IPPV include avoidance of one-lung anesthesia and its potential complications, minimal lung movement, and continued gas exchange in the manipulated lung (2). Our case showed adequate or improved gas exchange and hemodynamics during HFPPV as compared to IPPV. Although such stability has been demonstrated before, no reports of the use of HFPPV exist in which it was applied to a previously pneumonectomized individual in whom lung compression was required for successful surgical completion.

Oxygenation and carbon dioxide elimination were easily maintained in our patient, as were peak airway pressures. Previous studies utilizing HFV have demonstrated well maintained oxygenation and ventila-



Table 1 (continued)

Respiratory data						
PVR (dynes·sec·cm <sup>-5</sup> )	ABG (pH-Pco <sub>2</sub> -Po <sub>2</sub> )	MVBG (pH-Pco <sub>2</sub> -Po <sub>2</sub> )	Qs/Qt	RR (breaths/min)	EXP TV (ml)	Paw (cm H <sub>2</sub> O)
113	7.52-31-278	7.48-37-37	0.02	10	900	24.8
83	7.55-30-293	7.50-35-39	0.02	80	250	24.3
137	7.43-40-183	7.40-44-38	0.09	80	204	24.8
131	7.45-37-187	7.42-41-40	0.09	10	650	—
—	7.35-46-94 50% FiO <sub>2</sub>	7.31-55-42 50% FiO <sub>2</sub>		Spontaneous respiration		

tion; however, most authors have used lower peak and/or mean airway pressures with HFPPV (1-6). Simon et al. (9) found that lower peak airway pressures do not necessarily infer the presence of lower mean alveolar pressures. Chakrabarti et al. (10) demonstrated that with HFPPV the lowest peak airway pressures occurred between frequencies of 30-60 breaths/min. At rates above 100 breaths/min, the PEEP-like effect found with HFV increases significantly (10).

Hemodynamic parameters in our patient, including blood pressure, heart rate, right atrial, pulmonary artery pressures, cardiac index, and pulmonary vascular resistance, were not significantly different after switching from IPPV to HFPPV. Previous studies in animals and humans have shown variable changes in cardiovascular parameters during HFPPV. Most studies have demonstrated no change in blood pressure, heart rate, systemic vascular resistance, or cardiac index with HFPPV (10-12). Some report increases in cardiac index with HFPPV (13,14), but few report all hemodynamic variables concomitantly with pulmonary measurements. Only one study reports pulmonary shunt changes (13). Multiple different ventilator systems have been used for HFV and HFPPV. The comparison of hemodynamic and respiratory data between these systems may not be valid due to differences in delivery systems, I:E ratios and expiratory resistances. IPPV was not utilized during the actual spine fusion so we cannot compare the gas tensions and hemodynamic findings at that time to HFPPV.

HFPPV offers certain advantages to the anesthesiologist over other methods of HFV such as HFJV or HFO. HFPPV allows for the delivery of potent inhaled anesthetic agents utilizing conventional vaporizers and scavenging systems. Intravenous anesthetics may be required for patients receiving HFO and HFJV and may be associated with delayed awakening (15). The use of 50% N<sub>2</sub>O and low dose isoflurane in our patient avoided depression of SSEPs that might have been encountered with some inhalation general anesthetic techniques utilized with HFJV or HFO

(16). A rapid change from IPPV to HFPPV can be made by merely changing the settings of the Siemens-Elema ventilator, as opposed to detaching and reattaching different equipment necessary for initiation of HFJV or HFO. Waste gas can be easily and routinely scavenged with HFPPV, whereas new systems need to be engineered for scavenging during HFJV or HFO (4).

The Siemens-Elema 900D anesthesia machine is particularly well suited for HFPPV. No problems were encountered in switching our patient to this respiratory system because only minor changes in respiratory settings were required. Guidelines previously demonstrated for optimal tidal volume and rate to optimize CO<sub>2</sub> elimination were used in our pneumonectomized patient and adequate CO<sub>2</sub> elimination was confirmed.

In conclusion, the case presented represents a unique application of HFPPV utilizing the Siemens-Elema 900D ventilator. Use of such a system provided optimal operating conditions and hemodynamic and respiratory stability in this pneumonectomized man undergoing thoracotomy and further pulmonary compromise.

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## *Yersinia enterocolitica* and Transfusion-Induced Septicemia

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**Key Words:** INFECTION, transfusion-based.  
TRANSFUSION, *Yersinia* bacteremia.

In the United States over 50% of transfusions are administered in the perioperative period, usually by members of the anesthesia care team (1). Most anesthesiologists are, therefore, acutely aware of the variety of complications that can be associated with blood transfusions. These complications commonly consist of hemolytic, febrile, allergic, or metabolic responses. Transmission of infectious diseases is an acknowledged complication of transfusions. In this age of nonreusable blood collection equipment, the development of septic shock after blood transfusion is rare. However, we report a case of septic shock and endotoxemia resulting from the transfusion of blood contaminated with *Yersinia enterocolitica*.

### Case Report

A 61-year-old ASA III man with a history of hypertension and atherosclerotic peripheral vascular disease was taken to the operating theater for a right femoral-popliteal bypass grafting procedure. Past medical and surgical history was remarkable for an above-knee amputation performed 8 weeks earlier followed by an aortic-iliac bypass grafting procedure 2 weeks before the present operation. The patient's only medications were allopurinol and hydrochlorothiazide. Recovery from previous surgery was unremarkable until the development of right lower extremity pain necessitated another operation. Hematocrit at that time was 31%.

Anesthesia was induced with fentanyl 5  $\mu\text{g/kg}$  and thiopental 2.5  $\text{mg/kg}$ , followed by succinylcholine 100  $\text{mg}$ ,  $\text{O}_2$ , and tracheal intubation. Anesthesia was maintained with fentanyl, isoflurane, pancuronium,

$\text{N}_2\text{O}$ , and  $\text{O}_2$ . Monitoring included a  $\text{V}_5$  ECG, esophageal stethoscope with temperature probe, blood pressure cuff, arterial and right internal jugular central venous pressure lines, and urinary catheter. Two units of CPD-A (citrate-phosphate-dextrose-adenine) preserved packed red blood cells were transfused during the course of the surgery to replace a 1200-ml estimated blood loss. The red blood cells were given without significant delay after their arrival in the operating room. Approximately 45 minutes after the second unit of blood had been given, the patient developed hypotension, tachycardia, and oliguria. Before this the patient was hemodynamically stable with urine output  $>1 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ . With this change in hemodynamic status, there were no signs of ischemia on the  $\text{V}_5$  ECG and no evidence of hemoglobinuria, urticaria, temperature change, or change in peak airway pressure. An arterial blood specimen had a pH of 7.26,  $\text{Po}_2$  of 60 mm Hg,  $\text{Pco}_2$  of 51 mm Hg, and base excess of  $-3.5 \text{ meq/L}$  at an  $\text{FiO}_2$  of 0.5. Minute ventilation was increased in response to the respiratory acidosis,  $\text{N}_2\text{O}$  was discontinued, and 5 cm  $\text{H}_2\text{O}$  positive end expiratory pressure was added. When the hypotension continued to be refractory, the isoflurane was also discontinued. An IV bolus of electrolyte solution increased the central venous pressure to 12 mm Hg from 9 mm Hg. In spite of the hydration the arterial blood pressure remained 70–80 mm Hg with a heart rate of 120 beats/min. Ephedrine in 5-mg increments and phenylephrine in doses of 40–80  $\mu\text{g}$  were unsuccessful in raising the blood pressure. The central venous pressure line was replaced by a Swan-Ganz catheter. The initial pulmonary capillary wedge pressure was 10 mm Hg, central venous pressure, 10 mm Hg; cardiac output, 7.2 L/min; and systemic vascular resistance calculated to be  $470 \text{ dynes}\cdot\text{sec}^{-1}\cdot\text{cm}^5$ .

The hemodynamic profile obtained with the Swan-Ganz catheter was highly suggestive of sepsis. The

The following case occurred in the Anesthesia and Operative Service at Walter Reed Army Medical Center, Washington, D.C.

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intravenous solution bags, solution administration sets, individual blood bags, and samples of the patient's blood were all sent for culture. Prior antibiotic therapy included cefoxitin 2 g, IV given prophylactically at the start of the case. This coverage was broadened to include IV clindamycin 600 mg and amikacin 400 mg. Methylprednisolone 2.5 g was given IV and a dopamine infusion was started (initially at a rate of  $3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ). With dopamine the cardiac output increased to 10 L/min but the patient remained hypotensive. A phenylephrine infusion was without effect and was changed to norepinephrine  $0.05 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ , which maintained systolic blood pressure at 100 mm Hg. The patient was transferred to the surgical intensive care unit where his cardiac output increased to 18 L/min despite cessation of the dopamine infusion. The systemic vascular resistance decreased to  $250 \text{ dynes}\cdot\text{sec}^{-1}\cdot\text{cm}^5$ , and the temperature increased to  $39.5^\circ\text{C}$ . Twenty hours later, an exploratory laparotomy revealed no obvious source of infection. Forty-nine hours after the femoral-popliteal bypass repair, the patient died in septic shock with multiple organ failure and disseminated intravascular coagulation.

The patient's plasma obtained after the transfusions contained 0.15–1.5 ng/ml endotoxin. Endotoxin assay was negative in healthy controls, as was a sample of the patient's plasma obtained before the transfusion. Four antemortem blood cultures grew *Yersinia enterocolitica*, as did both blood bags (I and II) and the blood administration set used to administer the two units. Subsequent interviews with donors I and II revealed that although both were asymptomatic at the time of donation, donor I had experienced a "flu-like" gastroenteritis in the weeks before blood donation. At the time of the interview (approximately 5 weeks after donation), donor I had antibody titers to *Yersinia enterocolitica* of 1:256. This had increased from 1:128 in plasma saved from the time of donation and subsequently tested, reflecting a recent *Yersinia* infection. Donor II had negligible antibody titers and the growth of *Yersinia enterocolitica* from blood taken from bag II was thought to be secondary to cross contamination by the blood administration set.

## Discussion

A wide variety of diseases can be transmitted by the transfusion of blood. Although viral diseases such as AIDS and hepatitis are currently thought of when infectious complications of blood transfusion are discussed, bacterial transmission can be just as deadly

and with more immediate consequences. The bacterial contamination of stored blood bags has decreased with the widespread use of disposable phlebotomy equipment and blood storage bags, special needles that avoid "coring" of skin plugs, and use of aseptic technique (2). With appropriate precautions, there is approximately a 2% incidence of blood contamination at collection, usually with nontoxic gram-positive organisms such as staphylococci and diptheroids. With cold storage at  $4^\circ\text{C}$  in citrated solutions, the growth of these skin contaminants is unlikely (3). Other potential avenues for bacterial contamination of blood are much less frequent. Many blood-banking facilities restrict blood donations from donors within 72 hours of dental extractions because upward of 85% of individuals develop a transient bacteremia after this type of dental procedure. Other causes of transient bacteremia include tooth brushing, oral irrigation, sigmoidoscopy, barium enema, and liver biopsy. A normal bowel movement is claimed to produce a 10% incidence of bacteremia, and it is said that constipation or rectal irritation may increase this percentage (2).

Bacteremia at the time of blood donation is rare and if present is usually cleared within a matter of minutes by the reticuloendothelial system or polymorphonuclear leukocytes. Blood collected during an episode of bacteremia due to gram-negative enteric organisms can result in growth in cold-stored, citrated blood. Psychrophilic organisms of enteric origin that include the coli-aerogenes group, pseudomonas and, in our patient, *Yersinia enterocolitica* thrive in citrated blood stored at  $4^\circ\text{C}$ , especially within a pH range of 5.6–7.6 (4). In the laboratory, the inoculation of 80 colony-forming units CFU/ml *Yersinia enterocolitica* organisms into a blood bag yielded 5 million CFU/ml after 21 days of storage at  $4^\circ\text{C}$ . Gram's stain did not demonstrate the organism, and visual inspection of the unit revealed no turbidity. Only overnight culture of a sample of the contaminated blood allowed the identification of this organism (5). Because transfusion of gram-negative-contaminated blood is implicated in the majority of fatalities due to contaminated stored blood, identification of these units takes on great importance.

*Yersinia enterocolitica* is an aerobic gram-negative rod and a facultative anaerobe. Clinical manifestations of yersinosis can include mesenteric lymphadenitis, meningitis, and colitis, but most commonly yersinosis presents as a mild, self-limited gastroenteritis with diarrhea and abdominal pain. Although the organism involved is generally sensitive to streptomycin, aminoglycosides, trimethoprim-sulfamethoxazole, chloramphenicol, tetracyclines, colistin, and



nitrofurantoin, the antibiotic of choice for treatment of yersinosis has not yet been determined because the results of antibiotic therapy in clinical situations have so often been highly variable (5). In very young, very old, and immunocompromised patients, this organism can cause septicemia with a 34-50% mortality, even with appropriate therapy (6,7). Five other cases of transfusion-induced *Yersinia* septicemia have been reported. Two patients had postpartum anemia, one was an octogenarian, one had metastatic disease, and one had alcoholic liver-pancreatic disease. Our patient had vascular disease, hypertension, and several operations in the days preceding his demise. Our case was the only example of the intraoperative administration of contaminated blood. Five of these six cases were fatal (5,8-10).

By history, one donor of the blood given to our patient had an episode of gastroenteritis, presumably *Yersinia*-induced. During a presumed episode of bacteremia, a unit of blood was donated. This unit of blood was stored in a CPD-A collection bag at 4°C, allowing the *Yersinia* contaminants to multiply. The resultant transfusion-induced septicemia was fatal in our case as it has been in 83% of the reported cases (5,8-10). In this case, the precautions taken in careful storage, typing, and cross-matching, rechecking accompanying paper work with the blood unit, and the patient's identification by several individuals, and visually examining the unit for turbidity and administration in a timely fashion, all necessary for the safe use of blood products, were all strictly adhered to. In spite of this, the administration of blood products in this case resulted in a fatal outcome. The administra-

tion of blood products carries various risks, including transmission of virally mediated infectious diseases. However, other equally as serious blood transfusion-related complications can occur. The possibility of bacterial contamination of blood products is a rare but potentially fatal complication, with immediate manifestations and often tragic results.

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## Letters to the Editor

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### Epidural Butorphanol for the Relief of Postoperative Pain

To the Editor:

We congratulate Abboud et al. (*Anesth Analg* 1987;66:887-93) for conducting a CO<sub>2</sub> challenge study on patients in the immediate postoperative period—certainly not an easy task to accomplish.

Last year we reported a study utilizing epidural butorphanol 4 mg for pain relief in nonobstetric patients after abdominal operations (1) and showed that epidural butorphanol provided pain relief with rapid onset (15 minutes) but substantially shorter duration (5.6 hours) than that of epidural morphine 5 mg. In a subsequent study (unpublished data) we found that, with serial arterial blood gas measurements, epidural butorphanol 4 mg did produce statistically significant elevation in P<sub>a</sub>CO<sub>2</sub> even though no clinically significant respiratory depression (respiratory rate 10 breaths/min) was observed in these patients. Our observation in nonobstetrical patients is similar to that reported by Abboud et al. However, we could not quite agree with the conclusion drawn by them: "An agent providing 6-8 hours of pain relief such as butorphanol in the present study, would be ideal, because patients could be kept in the recovery room for this time." In most instances, it would be impractical and emotionally distressing to keep patients in the recovery room for that long a period of time. On the contrary, the short duration of action of epidural butorphanol would require more frequent administration, a distinct disadvantage from the manpower standpoint. Furthermore, as advocated by the authors, close observation for signs of respiratory depression associated with epidural butorphanol are definitely needed, which appears to negate the one presumed advantage of epidural butorphanol, namely lack of respiratory depression (2,3). Epidural butorphanol might be an interesting alternative to epidural morphine, but the search for an ideal spinal opiate for postsurgical pain still must be continued.

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### Winged Scapula Associated with Epidural Anesthesia

To the Editor:

Winged scapula produced by C5,6,7 radiculopathy or by long thoracic nerve neuropathy is occasionally seen after general anesthesia (1), but review of the literature and Bromage's (2) textbook revealed no reports associated with epidural anesthesia. A case associated with positioning during epidural anesthesia is presented.

A 26-year-old woman was referred for evaluation 7 days after delivery because of weakness of the right shoulder. Additionally, she had noticed protrusion of the right scapula with certain movements. In retrospect, she related her complaint to the epidural anesthetic for labor and delivery. The epidural had been performed with the patient lying on her left side, knees pulled up to the abdomen, and upper body and head and neck flexed on the abdomen as much as possible. During the procedure she experienced right shoulder pain and neck pain that disappeared on resuming the supine position. The epidural anesthetic was adequate, and labor and delivery were without complication. The next day, when more ambulatory and while combing her hair, she noticed weakness of the right shoulder. Neurologic examination revealed a winged scapula on the right side made more pronounced by forward flexion of the extended arm against resistance. Abduction of the arm was limited. The patient was referred for neurologic evaluation. Complete recovery occurred over a 6-month period.

Winged scapula (3), caused primarily by injury and occasionally by infection, results from dysfunction of nerve roots C5,6,7 or the long thoracic nerve, a motor nerve innervating the serratus anterior muscle. Injury may occur by direct trauma to the neck, by exerting strong downward force on the shoulder, by increasing the angle between the neck and the shoulder, or by any maneuver that stretches the nerve roots or nerve. The most common cause of injury

to the nerve during general anesthesia is putting the patient in the Trendelenburg position (4) with improperly applied padding, thereby causing the shoulder to be forcibly pushed down with overstretching of the long thoracic nerve. Although the patient believed that her injury was caused by the epidural anesthetic, a more likely cause was stress on the neck produced by the patient's assuming a commonly used position for induction of epidural (or spinal) anesthesia. Therapy consists of avoidance of further stress to the neck and serratus anterior muscle. Most injuries recover in 3-12 months.

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## Atracurium Pretreatment for Prevention of Succinylcholine Fasciculations

To the Editor:

We read with interest the recent paper by Sosis et al. (1), who compared atracurium and *d*-tubocurarine pretreatment for prevention of succinylcholine myalgia and also reported their efficacy in preventing fasciculations. Their Table 1 shows the incidence of fasciculations (mild and moderate) to be 79% in the saline (control) group of 14 patients, 46% in the atracurium pretreated group of 13 patients, and 12% in the 17 patients pretreated with *d*-tubocurarine. Their statistical analysis did not demonstrate, nor do their results report, a significant ( $P < 0.05$ ) difference between the saline and atracurium groups in prevention of fasciculations. This is surprising because Manchikanti et al. (2), using a similar protocol but with 20 patients in each group, did show such a difference at the  $P < 0.05$  level.

We reanalyzed the fasciculation data of Sosis et al. and, using Fisher's exact test (one-tail), found a difference in the incidence of fasciculations between the saline and atracurium groups at the  $P = 0.043$  level. This is reassuring because we commonly administer small doses of atracurium before succinylcholine and our clinical impression has been that it is effective in reducing the incidence of fasciculations.

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In Response:

We thank Herlich et al. for their interest in our report comparing atracurium and *d*-tubocurarine for the prevention of succinylcholine myalgia (1). Herlich et al. state that our "statistical analysis did not demonstrate a significant ( $P < 0.05$ ) difference between the saline and atracurium groups in the prevention of fasciculations." We are pleased that their statistical analysis shows that this difference is indeed a significant one because we clearly stated in our summary "... ATR (atracurium) is significantly better than NS (saline) for the prevention of fasciculations."

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## Effect of Age on Maximum Circulating Local Anesthetic Concentrations during Epidural Anesthesia

To the Editor:

Finucane et al. recently reported the effect of age on maximum blood concentrations of lidocaine during lumbar epidural anesthesia (1). They concluded that "the mass of local anesthetic solution should be reduced in elderly patients undergoing epidural anesthesia because there is a greater segmental spread, and serum levels of local anesthetics are increased." That segmental spread is greater in older patients has been reported previously by several authors (2-4), and we agree with that aspect of their conclusion. However, we disagree with the recommendation that the initial dose of epidural anesthetic be reduced in older patients because of higher serum levels. Finucane et al. did not discuss the results of three previous reports that disagree with their conclusion (5-7; Table 1). In these previous reports, single injections of a variety of doses of lidocaine and bupivacaine, with and without epinephrine, were given by the lumbar and caudal epidural routes. In none of these reports was there a statistically significant difference between age groups and the maximum blood levels of local anesthetics, or the time for achieving maxi-

Table 1. Maximum Local Anesthetic Concentrations during Peridural Anesthesia

	Freund et al. 1984	Freund et al. 1984	Bowdle et al. 1986	Veering et al. 1987	Finucane et al. 1987
Drug	Lidocaine	Bupivacaine	Lidocaine	Bupivacaine	Lidocaine
Dose	6 mg/kg	2.2 mg/kg	400 mg	95 mg	4 mg/kg
Epinephrine	Yes	Yes	Yes	No	No
Route of administration	Caudal*	Caudal*	Lumbar	Lumbar	Lumbar
Age, younger group	32 ± 5.2	27 ± 7.0	32 ± 5.2	36 ± 11	25 ± 3.3
Age, older group	66 ± 5.3	69 ± 10	65 ± 6.9	70 ± 8	69 ± 6.4
Maximum concentration (Cm) younger group (mcg/ml)	2.47 ± 0.73	0.86 ± 0.22	1.84 ± 0.81	0.53 ± 0.15	2.73 ± 0.68
Maximum concentration (Cm) older group (mcg/ml)	2.61 ± 1.45	0.69 ± 0.25	2.28 ± 0.90	0.47 ± 0.12	3.29 ± 1.34
Time of Cm, younger group (min)	45†	30†	45‡	20§	?
Time of Cm, older group (min)	25†	20†	45‡	26§	?

\*Drug injected through a catheter advanced to the L5-S1 level.

†Time of peak, mean concentration.

‡Median time of peak.

§Mean time of peak.

mum blood concentrations. Moreover, the differences in local anesthetic blood concentrations between age groups were of no clinical significance, because the concentrations were low, and there was no toxicity. The data of Finucane et al. are not substantially different from the previous reports, because there was neither a statistically nor a clinically significant difference in maximum blood concentrations. Finucane et al. reported a statistically significant difference in the time to peak blood levels, but the magnitude of the difference is difficult to interpret because the actual times are not given, only whether the time was less than or greater than 10 minutes. In any case, the clinical significance of the maximum blood concentrations occurring at an earlier time is doubtful.

We maintain that a *single* dose of epidural local anesthetic need not be reduced in older patients on account of the resulting circulating local anesthetic concentration. The studies cited show that the maximum blood local anesthetic concentration is not significantly affected by age, and that maximum blood concentrations are low and not associated with toxicity. However, when *multiple* doses of local anesthetic are administered, accumulation of toxic concentrations may occur in older patients because of decreased local anesthetic clearance (6,7). Inoue et al. have discussed pharmacokinetic simulation of epidural lidocaine reinjection (8), and we have illustrated local anesthetic toxicity in an elderly patient by pharmacokinetic simulation of multiple reinjections of a lumbar epidural catheter with lidocaine (6). Drug interactions may also result in decreased local anesthetic clearance. Many older patients receive  $\beta$ -adrenergic blocking drugs for treatment of hypertension or angina, drugs known to reduce the clearance of lidocaine (9) and bupivacaine (10).

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## In Response:

Thank you for the opportunity to respond to Bowdle and Freund's critique of our article. We did indeed state that serum levels of lidocaine were elevated in elderly patients after epidural injections; however, we also clearly pointed out that *P* values were equal to 0.06 (1). We believed that it was important to rule out a type II error, so we subjected these data to a power analysis, the results of which strongly suggest that these data would differ significantly if we expanded our series. So, we merely raised the possibility that our negative results might have been misleading.

Bowdle et al. seemed reluctant to entertain even the possibility that there may be an age-related difference in  $C_{s_{max}}$  based on the findings in three previous studies. Freund et al. (2) studied the influence of age on plasma



levels of bupivacaine and lidocaine, both with epinephrine, after caudal injections. That study does not compare with ours for two reasons: first, epinephrine-containing solutions were used by them and, second, the injections were administered via a catheter inserted into the caudal canal. There is no guarantee that catheters advanced 10 cm into the caudal canal will consistently end up in the lumbar epidural space.

In our study, lidocaine was injected via an 18-gauge Hustead needle consistently at the L3-4 interspace. Bowdle et al. (3), in a similar study of epidural anesthesia and age, again used epinephrine-containing solutions but also used doses of local anesthetic drugs that were not administered on a milligram per kilogram basis. Finally, Veering et al. (4) studied the effect of age on  $C_{p_{max}}$  after epidural injections of bupivacaine and found no significant difference. In this instance, a different local anesthetic was used. We suggest that the absorption pharmacokinetics of bupivacaine after epidural injection may be completely different from those of lidocaine. All three studies cited by Bowdle suffer from the same shortcomings as our study in that the numbers of patients studied in each series was quite small. Furthermore, in Bowdle's and Freund's studies, there was considerable imbalance numerically between patients in the young and old groups, e.g., in Bowdle's study there were 9 patients in the younger age group and 33 in the older, while in Freund's study there were 6 patients in the younger group and 16 in the older group.

Bowdle et al. also raised a question about our observations that  $C_{s_{max}}$  occurred early in elderly patients after epidural injections of lidocaine. The reason we did not specify the time other than before or after 10 minutes was because we did not measure blood levels of lidocaine at 15 minutes. At the 10-minute interval, 14 of 18 older patients had achieved  $C_{s_{max}}$ , whereas only 1 of 18 did so in the younger age group. At 20 minutes, 17 out of 18 in the younger age group had achieved  $C_{s_{max}}$ . We had no way of estimating when  $C_{s_{max}}$  took place in the younger age group other than sometime between 10 and 20 minutes. We tried to resolve this problem by measuring blood levels of lidocaine in eight patients in the younger age group at 15 minutes. In them,  $C_{s_{max}}$  occurred at 15 minutes in two of eight patients. We thought we had discussed this question quite well in the paper.

Bowdle et al. also questioned the clinical significance of an earlier  $C_{s_{max}}$  in elderly patients. We cannot disagree except to say that the fact that it is earlier lends credence to the theory that the increased hydrostatic pressure in the epidural space (5) after injection of local anesthetic solutions in elderly patients may contribute to the rapid uptake of local anesthetics into the circulation.

Finally, we are grateful to Bowdle et al. for raising these questions. To our knowledge, no one has tried to separate out the possible influence of epinephrine on the absorption

kinetics of local anesthetics injected epidurally in different age groups.

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3. Bowdle TA, Freund PR, Slattery JT. Age dependent lidocaine pharmacokinetics during lumbar peridural anesthesia with lidocaine hydrochloride or lidocaine hydrochloride. *Reg Anaesth* 1986;11:123-7.
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## Use of Breathing-Circuit Stethoscopes Can Have Complications

To the Editor:

I read with interest the letter of Kainuma and Shimada (1) describing a breathing-circuit stethoscope, which they devised and recommended for situations not suitable for use of a precordial or esophageal stethoscope. Their points are well taken, but I think it important to mention two potential sources of complications attributable to the breathing-circuit stethoscope they described. These are, first, the potential for endotracheal tube dislodgement, resulting from the anesthesiologist being physically connected to the patient's airway during use of this apparatus and, second, the creation of another connection within the breathing circuit, which adds an additional site for a circuit disconnection.

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## Book Reviews

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### Clinical Monitoring Practice, 2nd Ed.

Gravenstein, J. S., D. A. Paulus. Philadelphia: Lippincott, 1987, 446 pp, \$49.50.

Monitoring has become a major task (some would say *the* major task) of contemporary anesthesia practice. With the increasing complexity and length of surgery and with chronic illness becoming commonplace in an aging population, the challenge to give safe passage to a comatose, paralyzed patient through a risk-prone operation is greater than ever and growing. It is now abundantly clear that the anesthesiologist's unaided senses, while necessary, are not sufficient to meet today's challenge. A host of monitoring devices and methodologies designed to extend our senses is now available. The 1970s gave us invasive methods; noninvasive monitors have developed in this decade. But the very number and variety of available monitoring devices is now a problem. Can they be trusted? Will they confuse? Will they distract us so much that we will neglect our patients?

Gravenstein and Paulus provide answers in their tightly constructed but comprehensive book, *Clinical Monitoring Practice*. "Instruments," they assert in an introductory chapter, "were designed to allow the clinician to spend more time, rather than less, observing the patient." To know when a monitor can be trusted (and when it cannot), to avoid confusion and distraction in their use, monitors must be understood. This book delivers a detailed explanation on how monitors work. Just about every major class of monitoring instrumentation used in anesthesia today is covered. Each chapter begins with a concise review of physiologic and methodologic principles, and then describes the instrumentation in sufficient detail for understanding, without getting into the blueprints.

As expected, the cardiovascular and respiratory chapters receive a major share of the space. But the nervous system is well covered with descriptions of processed EEG and evoked potential instrumentation, and intracranial pressure recording is described. Temperature and neuromuscular function are included, as well as fluids and electrolytes, and fetal monitoring. Throughout, line drawings supplement the text and add clarity. Every chapter except one ends with a useful bibliography. The exception is acid-base and blood gas measurement, an omission, one hopes, that will be corrected in a future edition. Interestingly, pulse oximetry merits only a page and a half; I suspect that much of the literature on this subject has emerged too recently to be included.

Many little "tricks" and aids are mentioned in addition to the necessary physiology and engineering. For instance, I was delighted to learn how a precordial stethoscope can

be kept in place with a 250-ml plastic IV solution bag. In the chapter on blood pressure monitoring, "ringing" and damping are lucidly described. The chapter on fetal monitoring is enriched by a description of the Apgar score.

The authors allege in the preface that the book is "short on theory and long on the dos and don'ts." True, but they also include a lot of philosophy and common sense. There are chapters on alarms and computers, and safety and maintenance. The chapters on monitoring without mechanical or electronic instrumentation and the anesthesia record are true gems in conveying the rationale of monitoring.

This is, happily, not your typical multiauthored text. Gravenstein and Paulus did it all, with a consistent and readable style and a refreshing lack of repetition and overlap. Yet the book encompasses a wealth of technical detail that for the most part is competently described. One can find an occasional quibble (I prefer "cerebral swelling" to their "cerebral edema" as the cause of acutely increased intracranial pressure) but this is a negligible price for a compact, comprehensive and up-to-date text. For contemporary practitioners of anesthesia, this is an important book.

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### Problems in Obstetric Anaesthesia.

Barbara Morgan, ed. Chichester: John Wiley, 1987, 198 pp, \$50.00.

This text contains clear concise writing by anesthetists who deal with their subjects on a daily basis. The book is meant to complement basic texts by placing emphasis on medical and anesthetic complications frequently encountered on the labor floor. Subjects covered include general and regional anesthesia, shock, aspiration, amniotic fluid embolism, cardiorespiratory disease, and fetal-neonatal effects of drugs. Two chapters in particular are well worth reading. "Anesthesia and Maternal Death" provides the most complete available review on this important subject. Based on the only reliable epidemiologic data (Confidential Enquiry Into Maternal Death in England and Wales), the chapter offers detailed critical event analysis allowing the reader access to those factors involved in nearly every anesthetic associated with maternal death. Concrete and relevant recommendations are made based on the data that can be applied to everyday practice to avoid maternal morbidity and mortality. "Complications of Epidural Anaesthesia" is

simply written and extensively detailed. We highly recommend it for those who wish to refresh their knowledge of methods to assure safe conduct of epidural block.

In contrast, some chapters appear to lack scholarship or credibility. To read the chapter "Problems of Analgesia in Labor" prompts the question: why does the author (and editor) choose to practice an art she considers so deleterious to labor, mother, and fetus? I cite only a few descriptive statements: "Epidural . . . is at times given early in labour . . . based on a mistaken concept that every labour needs analgesia . . ."; "It has consistently been reported that some small number of mothers feel deprived of the experience of childbirth as a result possibly of the very excellence of the analgesia." (Epidural analgesia's) attendant high forceps rate can cause a higher rate of maternal complications such as trauma to the genital tract and traumatic intracranial hemorrhage in the newborn"; (With epidural block) second stage is prolonged and there appears to be an increase in forceps rate in primiparae with single cephalic presentation." The author's remarkably biased presentation propagates popular misconceptions about epidural block and its effect on labor based on poorly designed studies and traditional misinformation no longer accepted by informed anesthesiologists. There are no prospective randomized studies in humans showing a cause and effect relation between properly administered epidural anesthesia and forceps use or duration of labor. Indeed there is much evidence that in similar populations with similar fetal head presentations, there is little or no difference in forceps rate or duration of second stage labor with or without epidural block. The author's emphasis on women who prefer to suffer in labor over the choice of analgesia appears to portray her professional indifference to pain, and ignores the majority (more than 80% in a recent survey) who indicate a desire for pain relief. This chapter represents a serious misrepresentation of the safety and advantages to mother and fetus of epidural block in labor and significantly detracts from the quality of the book.

The chapter titled "Severe Preeclampsia and Eclampsia" is evidence that old prejudices die hard. Essentially ignoring current understanding of this disease, the author downplays well-known studies that demonstrate the safety of epidural anesthesia in preeclampsia. The remarkable statement "general anesthesia is preferred to epidural . . . anesthesia for cesarean section" disregards a large body of evidence that shows skilled epidural for cesarean in the presence of this disease protects the mother from severe pulmonary and cerebral hypertension and provides a more favorable intrauterine environment. The author argues without documentation that hypotension after epidural block in preeclampsia is uncontrollable and that the extent of block required is too great. This transparent *mea culpa* gives fellow anesthetists little credit for clinical ability and wrongfully encourages the belief among clinicians, despite a lack of evidence, that epidural anesthesia in preeclampsia is to be avoided. Indeed the logical conclusion of these recommendations is that the anesthetist keep hands off until the severity of the disease requires emergency induc-

tion of general anesthesia, a choice that results in risks that are equal if not greater than those from regional block. The reviewers consider this chapter unacceptable in light of prevailing anesthesia practice and that those who espouse its merits may unwittingly promote a deterioration in the anesthetic care of the preeclamptic mother and fetus. In summary we highly recommend parts of this monograph but withhold our unreserved endorsement.

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### Obstetric Analgesia and Anaesthesia I & II.

Gerard W. Ostheimer, ed. in *Clinics in Anaesthesiology*. Philadelphia, WB Saunders, 1986, v4, #1&2, 444 pp. \$25.95/vol.

This two-volume book is intended to present the practicing anesthesiologist or trainee with a concise overview of obstetric anesthesia and to serve as a teaching and reference guide. Topically rather than conceptually oriented, the chapters are short and written for the most part by experts in the field. While some chapters go into great detail, others serve as quick reviews. Major issues are discussed and well referenced, with an occasional subject presented in a style that reflects the opinion of the writer.

Many sections are outstanding examples of the art of writing and contain information hard to find elsewhere. "Pain of Parturition" describes the anatomic, biochemical, and psychologic basis for the pain of labor, the physiologic risks induced by pain to the mother and fetus, and the maternal-fetal protective function served by analgesia during labor. "Toxicity of Local Anaesthetics I, II, & III" provide a rational and scientific analysis of the controversy surrounding the use of bupivacaine and 2-chloroprocaine and give guidelines for the continued safe use of these drugs in obstetric anesthesia. "Failed Intubation Protocol" presents a methodical approach to this potentially disastrous clinical situation in a well thought-out "drill" sequence that clinicians in the United States should consider adopting.

In contrast, we did not like the content or message of some sections. We were amazed to find "Pregnancy Induced Hypertension and Anesthetic Management" coauthored by an obstetrician who is also a well-known opponent of the use of epidural block in preeclampsia. The authors believe in minimal anesthesia involvement during labor and the use of local infiltration for delivery. A substantial part of the chapter is devoted to describing the induction of general anesthesia while the section on epidural anesthesia is short and timid in tone. Little space is given to the plentiful evidence for the safe use of epidural anesthesia in pregnancy-induced hypertension and the well documented protection conferred by epidural block to

both the mother and fetus. Fluid management issues in preeclampsia are superficially and inadequately dealt with. The unstated message in this chapter is, "Anesthesiologists do not understand fluid management in preeclampsia and are unable to avoid maternal hypotension and its adverse effects on the fetus." This sad non sequitur is analogous to telling obstetricians that they are unable to reliably treat pregnancy-induced hypertension and have little ability to control blood loss during surgery. In our opinion, both the tone and notions contained in this chapter considerably weaken the value of the book.

The chapter on intraspinal narcotics provides an informative basis for the neuropharmacologic action of opiates but is disappointing because the author does not encourage the routine use of postcesarean analgesia with epidural morphine. This circumspect opinion gives little credit to the many large series demonstrating the safe use of postcesarean epidural morphine and evidence that it is a clearly superior technique for postoperative analgesia.

There is no chapter devoted to major conduction anesthesia for labor and the subject is consequently discussed occasionally and in a fragmentary fashion. An overview of epidural analgesia for labor would seem appropriate given the stated intentions for this book.

The book presents a wealth of useful information and opinion from well-known authorities and on this basis deserves strong consideration for inclusion in one's library. The work falls short as a primary reference text for the practicing anesthesiologist or trainee.

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### The Age of Miracles, Medicine & Surgery in the Nineteenth Century.

Guy Williams, Chicago: Academy Chicago Publishers, 1987, 234 pp, \$8.95.

While this paperback book reviews the great advances in medicine and surgery during the nineteenth century, many of these advances were based on work that began in the eighteenth century or came to fruition in the twentieth century and these time periods are also covered. The opening paragraph points out that "... before the end of the eighteenth century irremedial pain was part of the human condition ... (whereas) ... By the end of the nineteenth century, pain had become less inevitable, and could be to some extent controlled." Perhaps that accomplishment is the most telling for those of us who specialize in the management of problems in pain relief regardless of their cause.

In anecdotal yet scholarly format, 16 advances ranging from anatomy ("body snatchers") and antiseptics, through

blood transfusion and nursing, to vaccination and x-rays, are reviewed in addition to anaesthetics. While the story of Morton and the ether dome as well as Crawford Long's accomplishments are well-known, the earlier contributions of Davy are presented in detail along with the latter accomplishments of Simpson and Snow as well as the ill-fated experiment of Toynebee who conclusively demonstrated in 1886, perhaps for the first time, that self-administration of anesthesia is fraught with hazard and can be lethal.

The chapters on blood transfusion and development of the nursing profession were especially entertaining and informative. The history of blood transfusion back to the seventeenth century is reviewed and the importance of research on anticoagulants between 1891 and the outbreak of the First World War to the clinical use of citrated whole blood in battle casualties highlighted. Florence Nightingale is credited with doing "... more than anyone else to change the appalling conditions in British hospitals ..." in the mid-nineteenth century. From her position as Superintendent of Female Nurses during the Crimean War she went on to a lifetime of training nurses who proceeded to upgrade the quality of patient care wherever they went. In summary, this book, which is as much social history as it is scientific and medical history, prevents an overview of the advances of the nineteenth century in a manner that permits one to appreciate, on reflection, the advances in this, the twentieth century, and to anticipate those of the twenty-first.

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### Advances in Oxygen Monitoring— International Anesthesia Clinics.

Kevin K. Tremper, Steven J. Barker, eds. Boston: Little, Brown, 1987, 239 pp, \$20.00.

This volume contains ten contributions or individual essays that could easily be read in any order. Its stated purpose is to review recent developments in O<sub>2</sub> measurement and to discuss future applications of new techniques. Established investigators have contributed reviews of emerging technologies; the chapters reflect the biases of the individual authors.

The book begins with a personal history of the oxygen electrode by Leland C. Clarke Jr, detailing experiments in his laboratory that led to the "Clarke electrode." This well written chapter contains a clear description of polarographic electrode function. The process behind a true scientific breakthrough makes for interesting reading and is not often encountered in the anesthesia literature.

A chapter on the theory of transcutaneous oxygen tension measurement includes copious discussion of models of skin blood flow and oxygen utilization that are extremely tedious and have little relevance to the average



clinician. On the other hand, Drs. Tremper and Barker's chapter on applications is a readable, well-referenced summary of current information. Although brief, the next chapter on conjunctival oxygen monitoring succinctly describes its advantages vis a vis transcutaneous techniques.

This chapter on mixed venous oxygen saturation monitoring consists mainly of case discussions. A bit more theoretical and practical information would have been welcome. The discussion of current models of  $Sv_{O_2}$  measuring devices is probably out of place in this volume.

Two chapters relating to pulse oximetry follow. The first is an outstanding description of how a pulse oximeter determines hemoglobin oxygen saturation and in my opinion was a bright spot in this volume. The following chapter thoroughly covered applications and limitations of the oximetry, but made for rather dull, if accurate, reading.

The next two chapters are concerned with oxygen optodes (oxygen-sensitive fluorescent indicator dyes), a technique of oxygen measurement that is still experimental. While the discussion of theoretical aspects may be overly detailed for a volume of this scope, these devices may become commonplace if they can be successfully applied to indwelling intra-arterial technology. The final chapter discusses in vivo monitoring of cerebral oxygenation and cytochrome oxidase redox state. This technique uses an infrared light source to determine the state of the copper atom of the terminal cytochrome. The chapter is a clearly written summary of the theory and problems with this innovative method which may be the first to monitor adequacy of oxygen delivery at the cellular level.

Clearly, our ability to measure oxygen has progressed incredibly in the last 30 years. This volume documents this progress. However, the writing style is generally uninspired and some of the information is more suited to physiologists than to practitioners of anesthesia. Therefore this book would be best used as a library reference source rather than part of an individual's collection.

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### Anesthesia for Renal Transplantation.

G. B. Graybar, L. L. Bready. Boston: Martinus Nijhoff, 1987, 272 pp, \$65.00.

Renal transplantation is the only true treatment for the syndrome of end stage renal disease (ESRD) and as anesthesiologists we are called upon to participate in this treatment both for organ harvesting and transplantation. We are also being ever more often called upon to give anesthesia for procedures for the placement of access cannulas for dialysis, which is the palliative treatment of this disease.

The forward of this monograph describing the anesthetic management for renal transplantation is appropri-

ately written by Dr. Leroy D. Vandam, who performed the anesthesia for the first successful allogenic kidney transplant in a human being 33 years ago. This is followed by a delightful history of the events that led up to this historic occasion. As with any multiauthored book there is an uneven quality of the chapters, but most are well-written and to the point.

Several of the chapters in the monograph deserve special mention. The chapter on the criteria for the determination of brain death as well as the preoperative and intraoperative management of the renal or multiorgan donor was excellent and prepares us for this potentially unsettling experience. Likewise the section on pediatric transplantation is a complete and helpful guide for the management of this patient only recently seen. In the section on "Other Procedures" there is an excellent discussion on the best choice of agents for "monitored anesthesia care" supplementing local anesthesia as well as a method for administration of a supraclavicular brachial plexus block for PTFE graft placement, which is well-described in a simple cookbook fashion. The bibliographies of all of the sections are up-to-date and many are exhaustive. The section on neuromuscular blocking agents answers the questions of what should I give and why. The practical considerations portion of the section on intravenous agents provided a helpful why?, why not?, and how to, discussion of the most commonly used intravenous agents. The "game plan" at the end of the book is a useful plan that systematically discusses the evaluation and anesthetic management of a patient with ESRD for allogenic transplantation or any major surgical procedure using the protocol devised at UAB, the home institution for the majority of the contributors.

There were a few disappointments as well. The chapter on medical management provides too short a discussion of immunosuppressive therapy, especially cyclosporine A and monoclonal therapy, and these deficiencies were not made up for by overlap from other authors. The chapters on the basic science and pharmacology are either not complete enough or do not clearly define the differences between normals and patients with ESRD. The chapter on monitoring was especially uneven. Twenty percent of the chapter was spent discussing arterial line placement, yet it did not discuss advantages and problems that can be encountered with noninvasive blood pressure monitoring.

The choice of anesthesia for transplantation and surgical procedures other than dialysis access is a difficult one because these patients most frequently have multiorgan disease and their volume status is unknown. While the discussion of the pros and cons of regional versus general anesthesia was extensive, much of the physiology discussed may only be valid for in situ kidneys and not for transplants onto the iliac artery. In the discussion of epidural anesthesia the side effects of lidocaine were discussed extensively, despite the fact that it is no longer the anesthetic of choice for long procedures, with no discussion of the effects and complications of long-acting drugs. I was especially disappointed that some of the reasons for choos-

ing general anesthesia were either not validated or put to rest once and for all in the text that followed.

On the whole, the book has many good sections that make it an easy reference for the management of patients with ESRD not only for transplantation but for all other surgical procedures. It will be a useful addition to the reference shelves of any institution that provides care for these patients.

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### Positioning in Anesthesia and Surgery, Second Edition.

John T. Martin, ed. Philadelphia: WB Saunders, 1987, 347 pp, \$45.00.

The second edition of *Positioning in Anesthesia and Surgery* improves the first by including better illustrations, a broader discussion of the literature, and more material. In 27 chapters, the 22 contributors cover the subject exhaustively. A few chapters review general topics: the physiology of erect and supine postures, neurologic and other complications due to positioning, and "unusual patients," such as infants, children, and parturients. The remaining chapters were organized in pairs, with each topic or position covered twice, once by a surgeon and once by an anesthesiologist.

The text offers more to praise than to criticize. Most important, the book is unique. Nowhere else is this essential information drawn together in such a useful form; most of us practicing anesthesia are aware of only a small fraction of it. Martin and his coauthors explore all aspects of positioning, ranging from a discussion of the physiology of cerebral blood flow in the Trendelenburg position to explicit directions on how to organize a team of OR workers to turn a patient into the lateral position. Although not all topics are covered in equal depth, and critical review of the large number of studies cited is sometimes lacking, little is omitted. The lists of references are extensive. To get the most from a book organized like this one, the reader relies on the index. This index is adequate, although an alphabetical list of positions by name would have been welcome.

Perhaps the best feature of the text is the art work. Uniformly done, excellent line drawings by Roy Schneider have replaced the mixture of photographs and drawings found in the first edition, to excellent effect. The drawings make clear the salient features of the equipment and the positions in a way that photographs could not.

While in some cases the issues of positioning do appear quite differently to parties on opposite sides of the ether screen, the redundant organization of the book is troublesome. The chapters by Day on orthopedic positioning and by Singh on the prone positions are invaluable. However, the majority of the brief surgical chapters contribute little that is not duplicated by the anesthesiologists writing on

the same subjects. Armboards are discussed in the three locations, for example. Multiple authorship produces wide disparities in writing styles, which range from lucid to prolix and obtuse. One author refers to the "up arm," while another calls it the "non-dependant arm." Some authors review the literature in much more depth than others. In all, loose editing is this book's greatest drawback.

In his preface, Dr. Martin makes it clear that he feels the advantages of his format outweigh the disadvantages. I disagree: more anesthesiologists and surgeons would read a shorter, more tightly edited volume. As it is, though, the much improved second edition of this unique book is invaluable. I will make it part of the reading for the residents on the orthopedic anesthesia service that I supervise. If you care for patients in the operating room you will do yourself and your patients a service by reading this book and applying its lessons.

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### Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Britt B, ed. *Malignant Hyperthermia*. Boston: Martinus Nijhoff Publishing, 1987, 420 pp, \$48.95.

Cook DR, Marcy JH. *Neonatal Anesthesia*. Pasadena, CA: Appleton Davis, 1987, 262 pp.

Dripps RD, Eckenhoff JE, Vandam LD. *Introduction to Anesthesia. The Principles of Safe Practice*. 7th Ed. Philadelphia: WB Saunders, 1987, 512 pp, \$29.00.

Dunn JM, ed. *Cardiac Valve Disease in Children*. New York: Elsevier, 1987, 370 pp, \$67.60.

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Foster PA, Roelofse JA. *Databook of Anaesthesia and Critical Care Medicine*. 4th Ed. New York: Springer Verlag, 1987, 204 pp, \$25.00.

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Larcon A, Laprevote-Heully M. *Urgences Medicales*, 3rd Ed., Paris: Masson, 1987, 308 pp, \$20.80.

Paris PM, Stewart RD, eds. *Pain Management in Emergency Medicine*. East Norwalk, CT: Appleton & Lange, 1987, 562 pp, \$59.95.

Pichlmayr. *EEG Atlas Anesthesia*. New York: Springer Verlag, 1987, 413 pp, \$129.00.

Ropper AH, Kennedy SK. *Neurological & Neurosurgical Intensive Care*. Rockville, MD: Aspen, 1987, 384 pp, \$52.00.

Safar P, Bircher NG. *Cardiopulmonary Cerebral Resuscitation*, 3rd Ed., Philadelphia: WB Saunders, 1988, 464 pp, \$18.50.

Severinghaus JW, Astrup PB. *History of Blood Gas Analysis*, Vol. 25, No 4 of *International Anesthesiology Clinics*. Boston, MA: Little, Brown, 1987, 224 pp, \$20.00 single issue or \$50.00 for annual subscription of four issues.

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Tremper KK, Barker SJ, eds. *Advances in Oxygen Monitoring*. Vol 25, No 3 of *International Anesthesiology Clinics*. Boston, MA: Little, Brown, 1987, 239 pp, \$20.00 single issue or \$50.00 for annual subscription of four issues.

Wilson GW. *Fifty Years, the Australian Society of Anaesthetists*. Australian Society of Anaesthesiologists. New South Wales, Australia: Edgecliff, 1987, 502 pp.

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- ☐ Original articles describe in 3000 words or less clinical or laboratory investigations.
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2. *Personal author(s) books and monographs*  
Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
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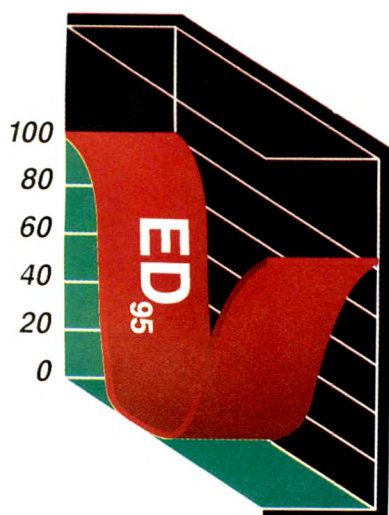
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This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINESTERASE REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anesthesia.

Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

### PRECAUTIONS:

**General:** Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells.

**Pregnancy: Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether the drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

### ADVERSE REACTIONS:

**Observed in Controlled Clinical Studies:** Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7.875 or 0.8%.


Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of  $\geq 0.60$  mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses  $\leq 0.30$  mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients.

**Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: *General:* allergic reactions (anaphylactic or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); *Musculoskeletal:* inadequate, prolonged block; *Cardiovascular:* hypotension, vasodilatation (flushing), tachycardia, bradycardia; *Respiratory:* dyspnea, bronchospasm, laryngospasm; *Integumentary:* rash, urticaria, injection site reaction.

<sup>1</sup>Hughes R: Atracurium: An Overview. *Br J Anaesth* 1986;58:2s-4s.

<sup>2</sup>Payne J: Atracurium, in Katz R (ed): *Muscle Relaxants: Basic and Clinical Aspects*. Orlando, Grune & Stratton, 1984, p 98.

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## The complete guide...

# NITROUS OXIDE/N<sub>2</sub>O

Editor: **Edmond I. Eger II, M.D.**,  
Professor and Vice Chairman for Research,  
Department of Anesthesia,  
University of California, San Francisco

After 140 years of use, nitrous oxide is now known to be more than an inert vehicle for other, more potent anesthetics. Nitrous oxide affects the function of every body tissue significantly. Optimum application requires a full appreciation of both the benefits and potential hazards of this anesthetic substance.

**Nitrous Oxide/N<sub>2</sub>O** is a complete resource on the subject. It describes what is known about nitrous oxide — applications and contraindications — and debates its continued clinical use. The current clinical applications of N<sub>2</sub>O are reviewed by means of:

- thorough discussion of N<sub>2</sub>O pharmacology and distribution
- detailed summary of known side effects and toxicity
- practical guidelines for avoiding and managing these effects

Finally, the case for administering this anesthetic is carefully and candidly assessed in chapters by proponents of both views. **Nitrous Oxide/N<sub>2</sub>O** is a controversial work that everyone using the drug will want to read.

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Eight full-time faculty positions at the Assistant/Associate/Full Professor level (title series, rank and salary commensurate with experience and qualifications). The positions require demonstrated experience in didactic teaching, clinical training, and patient care, with an established research interest. Applicants must have at least 4 years of postgraduate training, completion of an approved anesthesia residency plus a fellowship year or equivalent training in subspecialty area; board eligibility; meet California license requirements. Particular attention will be given to those having critical care, pain, OB/Gyn or ambulatory surgery training. Women and minorities are encouraged to apply. Send curriculum vitae, bibliography, and names of three references to John H. Eisele, Jr., M.D., Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. Position open until filled but not later than October 31, 1988. We are an Equal Opportunity/Affirmative Action Employer.

#### ARIZONA

The Department of Anesthesiology at the University of Arizona College of Medicine has openings for both clinical and tenure track faculty. Female and minority applicants are welcome. Applicants interested in an academic career should contact: Burnell R. Brown Jr, M.D., Ph.D., Department of Anesthesiology, Arizona Health Sciences Center, Tucson, AZ 85724. Equal Employment Opportunity/Affirmative Action Employer. Closing date: 6/30/88.

#### ANESTHESIOLOGY RESIDENTS

Royal College Fellowship certificate holders seeking entrance into the examination and certification system of the American Board of Anesthesiology are encouraged to apply for 1 year of clinical training in Anesthesiology at the CA-3 level at The University of Alabama at Birmingham. For further information, contact Director of Resident Education, Dr. James Boyce, Department of Anesthesiology, The University of Alabama at Birmingham, 619 South 19th Street, Birmingham, Alabama 35233 (telephone 205/934-6500). An Affirmative Action/Equal Opportunity Employer.

#### WISCONSIN: MEDICAL COLLEGE OF WISCONSIN

Department of Anesthesiology has an immediate opening for an individual with

primary interest in critical care medicine. Qualifications include ABA certification or Board eligibility, completion of a critical care fellowship and Wisconsin state licensure or eligibility. Applicants should have strong interest in clinical teaching and patient care. Research interest and background are desirable. Salary and level of faculty position will be commensurate with qualifications. Interested candidates should send CV to: Eugene Y. Cheng, M.D., Department of Anesthesiology, Medical College of Wisconsin, 9200 W. Wisconsin Avenue, Milwaukee, WI 53226.

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#### ANESTHESIOLOGIST: ASSISTANT PROFESSOR

Board certified or equivalent. Applicant must have at least one year experience as a research fellow preferably in respiratory physiology. Responsibilities include instruction of medical students, interns and residents in various aspects of anesthesiology, clinical service; clinical and/or basic science research; and publication of scholarly articles. Must be licensed or eligible for Texas licensure. The University of Texas Health Science Center, Department of Anesthesiology, 7703 Floyd Curl Dr., San Antonio, TX 78284. Equal opportunity employer.

#### DIRECTOR, OBSTETRICAL ANESTHESIOLOGY PROGRAM

At The University of Texas Health Science Center, San Antonio. Professor level with board certification or equivalent. Must have extensive research and teaching. Responsibilities include instruction of medical students, interns and residents in various aspects of anesthesiology; clinical service; clinical and/or basic science research; and publication of scholarly articles. Must be licensed or eligible for Texas licensure. Equal opportunity employer. Department of Anesthesiology, 7703 Floyd Curl Dr., San Antonio, TX 78284.

#### FLORIDA

Anesthesiologist-BC/BE, for one or two openings in private practice. Located southwest coast of Florida. Excellent opportunity to join well established group. All procedures. No open heart or pain clinic. Reply to Box NN54, c/o Anesthesia and Analgesia, 333 Cedar Street, New Haven, CT 06510.



#### PORTSMOUTH-HITCHCOCK MEDICAL CENTER

Section of Anesthesiology at the Portsmouth-Hitchcock Medical Center in Portsmouth, NH is seeking a Board Certified and Board Eligible anesthesiologist to join the faculty. Applicants should have formal training beyond the three-year continuum subspecialty of anesthesiology practice and have recognized skills in a subspecialty area of anesthesiology in lieu of formal fellowship training. Pain therapy or cardiovascular anesthesiology would be particularly desirable. The successful candidate must have a commitment to teaching medical students and residents in addition to clinical expertise. Ability and desire to do clinical and/or basic research is essential. Academic title and compensation consistent with experience. Submit curriculum vitae to: David Glass, M.D., Chief, Section of Anesthesiology, Hitchcock Clinic, Portsmouth-Hitchcock Medical Center, Portsmouth, NH 03756. An equal opportunity/affirmative action employer.

#### ILLINOIS

BC/BE anesthesiologist to join group of 7 MDs and 2 CRNAs in 400-bed community hospital—Chicago suburb. Active open heart service. Prefer recent graduate with regional anesthesia expertise. Curriculum vitae to CSS Associates, 6819 Winston Drive, Tinley Park, Illinois 60477.

#### ANESTHESIA INTENSIVIST

Anesthesia intensivist sought to join three other intensivists (2 medical, 1 surgical) in supervising a multidisciplinary academic Medical-Surgical ICU at Baystate Medical Center, an 878-bed regional referral center affiliated with Tufts University School of Medicine and with regional trauma and burn programs. Critical Care Program is supported by residents in medicine, surgery, anesthesiology and other specialties. Apply to Howard Trachtenberg, MD, Chairman, Dept. of Anesthesiology or Daniel Teres, MD, Chief, Adult Critical Care Program, Baystate Medical Center, 759 Chestnut Street, Springfield, MA 01199.

#### ANESTHESIOLOGY FELLOWSHIPS, SPECIALIZED YEAR, (PGY-5)

Applications are now being accepted for Anesthesiology Fellowships in the Department of Anesthesiology at the University of Massachusetts Medical Center in Worcester, Massachusetts. The Fellowship positions available are in the following areas;

Pain Control, Critical Care Medicine, Cardiovascular Medicine and Research. Interested candidates please submit curriculum vitae to Gary Welch, MD, PhD, Chairman, Department of Anesthesiology, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester MA 01655. UMMC is an equal opportunity/affirmative action employer.

#### ANESTHESIOLOGIST/ACADEMIC ANESTHESIOLOGISTS

Full-time academic positions available in a 416-bed teaching hospital for anesthesiologists with subspecialty fellowship training in cardiac anesthesia, chronic pain control or neuroanesthesia. Faculty rank commensurate with experience. Board certified candidates preferred. Send CV to: Sanford L. Klein, D.D.S., M.D., Department of Anesthesia, UMDNJ-Robert Wood Johnson Medical School, One Robert Wood Johnson Place, CN-19, New Brunswick, NJ 08903-0019. An equal opportunity/affirmative action employer.

#### MIAMI

ANESTHESIOLOGIST BC/BE to join group of 9 MDs with 6 CRNAs located in the Greater Miami Area. Excellent starting salary and benefits. Reply to Hialeah Anesthesia Group, P.O. Box 133430, Hialeah, FL 33013.

#### NEBRASKA, ANESTHESIOLOGY

The University of Nebraska Medical Center has faculty positions available for board certified/board eligible anesthesiologists. Academic rank and salary commensurate with education and experience. Fellowship training and/or experience in research and teaching desirable but not required. Experience in pain management, regional anesthesia, or obstetrical anesthesia an advantage. Candidates must be eligible for Nebraska medical licensure. Interested applicants should send curriculum vitae and two letters of reference to: Dennis F. Landers, M.D., Ph.D.; Interim Chairman; Department of Anesthesiology; University of Nebraska Medical Center; 42nd & Dewey Avenue; Omaha, Nebraska 68105. Affirmative Action/Equal Opportunity Employer.

#### DUKE UNIVERSITY

Faculty positions (2-4) at the instructor or assistant professor rank are available from

the present through September 1, 1988. New faculty candidates with a strong desire to conduct clinical research and teaching in an outstanding academic environment are invited to apply. The tenured faculty is committed to the long-term career objectives of our junior members. Applicants should note those subspecialties of anesthesiology with which they may prefer to affiliate at Duke. Minimum qualifications consist of a complete three-year residency and N.C. state licensure. Send a letter of career plans/goals and curriculum vitae to: W. David Watkins, M.D., Ph.D., Professor and Chairman, Dept. of Anesthesiology, and Professor, Dept. of Pharmacology, P.O. Box 3094, Duke University Medical Center, Durham, North Carolina 27710. For further assistance or information call Mrs. Rosemary Cumbie, 919-681-2498. Duke University is an EO/AA Employer.

#### CHIEF ANESTHESIOLOGIST \*\*\* MAINE \*\*\*

Exciting opportunity for BC/BE Anesthesiologist at Rumford Community Hospital, a 97-bed community hospital affiliated with a 250-bed medical center. Community of 8,000+ offering a quality four-season lifestyle, affordable housing, and easy access to coast, mountains, rivers, and lakes. For additional information please forward CV to Box NN53 c/o *Anesthesia and Analgesia*, 333 Cedar Street, New Haven, CT 06510.

#### ANESTHESIOLOGIST—Full-Time faculty position

available for Board eligible anesthesiologist with fellowship training in a sub-specialty area (obstetrical; anesthesia, cardiac anesthesia, or neuro-anesthesia). Faculty rank will be commensurate with experience. Duties include patient care, teaching and research. Send CV to Christer Carlsson, MD, Professor and acting Chairman, Dept. of Anesthesiology, Temple University School of Medicine, Broad & Ontario Sts., Philadelphia, PA 19140. Equal Opportunity/Affirmative Action Employer.

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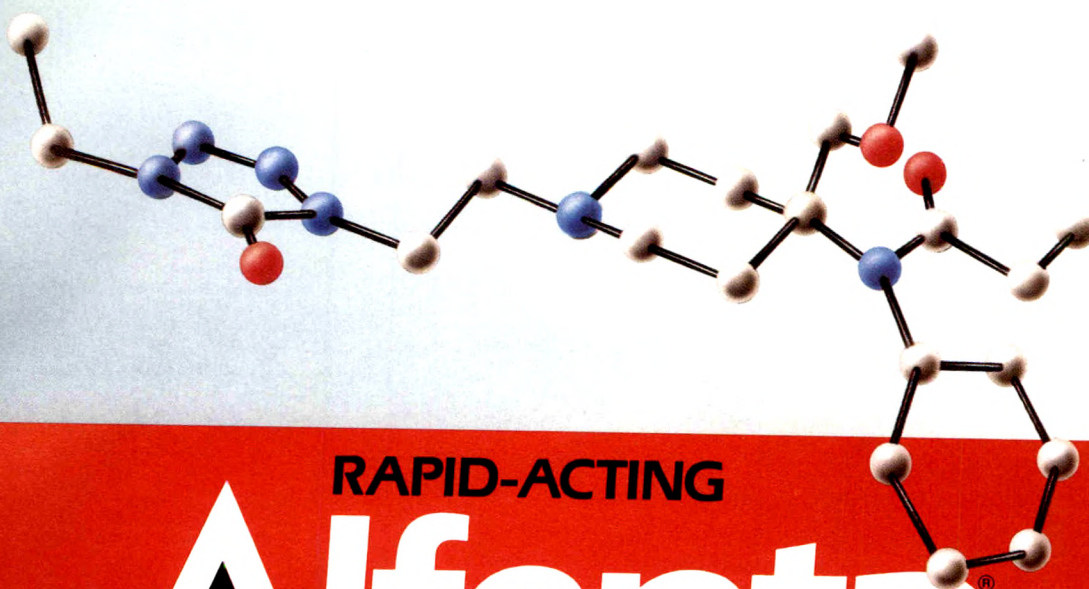
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for short procedures lasting up to 30 minutes  
in spontaneously breathing patients, or for procedures  
lasting 30 to 60 minutes in intubated patients

### **CONTINUOUS INFUSION**

for procedures lasting more than 45 minutes  
in intubated patients

\*As with other opioids, hypotension and bradycardia have been reported.

†As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained.

The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery. Skeletal muscle rigidity is related to the dose and speed of administration of ALFENTA. Dosage should be individualized in each case.

See following page for brief summary of Prescribing Information.

# Alfenta®

(alfentanil HCl) Injection II

## AN OPTIMAL OPIOID ANESTHETIC FOR MOMENT-TO-MOMENT CONTROL

### BEFORE PRESCRIBING, PLEASE CONSULT COMPLETE PRESCRIBING INFORMATION, OF WHICH THE FOLLOWING IS A BRIEF SUMMARY.

#### CAUTION: Federal Law Prohibits Dispensing Without Prescription

**DESCRIPTION:** ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-6.0.

**CONTRAINDICATIONS:** ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

**WARNINGS:** ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS.

AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE.

BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION, MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY.

ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg, following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg).

The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

**PRECAUTIONS:** DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

**General:** The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight.

In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients.

In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged.

Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery.

Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods.

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance.

Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO<sub>2</sub> stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO<sub>2</sub>. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

**Head Injuries:** ALFENTA may obscure the clinical course of patients with head injuries.

**Impaired Respiration:** ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

**Impaired Hepatic or Renal Function:** In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

**Drug Interactions:** Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical experience indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction.

Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

**Pregnancy Category C:** ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

**Nursing Mothers:** In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

**Pediatric Use:** Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

**ADVERSE REACTIONS:** The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported.

The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and non-disturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

	ALFENTA (N = 785) %	Fentanyl (N = 243) %	Thiopental Sodium (N = 66) %	Enflurane (N = 55) %	Halothane (N = 18) %	Saline Placebo* (N = 18) %
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypotension	10	8	7	7	0	0
Hypertension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall Rigidity	17	12	0	0	0	0
Skeletal Muscle Movements	6	2	6	2	0	0
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative Respiratory Depression	2	2	0	0	0	0
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/ Postoperative Sedation	2	8	2	0	0	6
Blurred Vision	2	2	0	0	0	0

\*From two clinical trials, one involving supplemented balanced barbiturate/nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were:

Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching.

Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

**DRUG ABUSE AND DEPENDENCE:** ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

**OVERDOSAGE:** Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD<sub>50</sub> of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression.

The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hypoventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

**DOSE AND ADMINISTRATION:** The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

Manufactured by Taylor Pharmacal Co. for



**JANSSEN  
PHARMACEUTICA**

Janssen Pharmaceutica Inc.  
Piscataway, NJ 08854

U.S. Patent No. 4,167,574  
March 1987 49-7619901-M



## Anesthesiologist/Pain Specialist

Department of Anesthesiology at the University of Rochester is seeking a faculty candidate with special interest and training in Pain Management. Our Pain Treatment Center is a multidisciplinary program, which is expanding its services.

The person must be committed to excellence in clinical care, teaching and clinical or basic science research. An individual who has completed ABA Certification and a Pain Fellowship is preferred. Academic rank and salary will be commensurate with qualifications.

New York State License is necessary.

Send Curriculum Vitae to:

**Ronald A. Gabel, M.D.**  
**Professor and Chairman**  
or  
**Jaimala Thanik, M.D.**  
**Medical Director, Pain Treatment Center**  
**Box 604**  
**University of Rochester Medical Center**  
**601 Elmwood Avenue**  
**Rochester, New York 14642**

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## PEDIATRIC ANESTHESIOLOGIST

Pediatric anesthesiologist needed to join a three-MD/two-CRNA staff of university affiliated children's hospital. Requirements include: fellowship or experience in pediatric anesthesia and board certification or eligibility. Full spectrum of pediatric anesthesia performed except open heart. Responsibilities include clinical anesthesia as well as resident and CRNA education and supervision.

We are located on the southeastern Virginia coast within easy access to beaches and resort cities. The hospital serves a regional population of over one million in both North Carolina and Virginia.

Salary is commensurate with appropriate training and experience and is complemented by an excellent benefit package.

For more information contact:

**William C. Petersen, MD**  
**Director; Pediatric Anesthesia Department**  
**Children's Hospital of The King's Daughters**  
**800 West Olney Road, Room #327**  
**Norfolk, Virginia 23507.**

Second International

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**Social Activities:** A cocktail hour has been planned the first night highlighting the exhibits. Also, participants of the Congress will float down the Cumberland for a dinner cruise on the General Jackson Show Boat.

**Sponsored by:** Department of Otolaryngology—Head and Neck Surgery and the Division of Continuing Medical Education. Congress Directors: Robert H. Ossoff, D.M.D., M.D., James A. Duncavage, M.D.

**Tuition:** \$425 after March 1, 1988  
\$375 before March 1, 1988  
\$200 residents  
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**Additional Information:** Vanderbilt Division of CME, Laser Congress Coordinator, CCC-5326 MCN, Nashville, TN 37232. (615)-322-4030.

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